cited in the European Search Report of EP00 98 3862.4
Your Ref.: PF220 PCT 2EP

#21 attachment
09/926348

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C12N 15/12, C07K 14/47, C12N 15/79, 5/10 A2

(11) International Publication Number: WO 99/18203

(43) International Publication Date: 15 April 1999 (15.04.99)

(21) International Application Number: PCT/JP98/04475

(22) International Filing Date: 5 October 1998 (05.10.98)

(30) Priority Data:
9/276271 8 October 1997 (08.10.97) JP

(71) Applicants (for all designated States except US): SAGAMI CHEMICAL RESEARCH CENTER [JP/JP]; 4–1, Nishi–Ohnuma 4–chome, Sagamihara–shi, Kanagawa 229–0012 (JP). PROTEGENE INC. [JP/JP]; 2–20–3, Naka–cho, Meguro–ku, Tokyo 153–0065 (JP).

(72) Inventors; and
(75) Inventors/Applicants (for US only): KATO, Seishi [JP/JP]; 3–46–50, Wakamatsu, Sagamihara–shi, Kanagawa 229–0014 (JP). YAMAGUCHI, Tomoko [JP/JP]; 5–13–11, Takasago, Katsushika–ku, Tokyo 125–0054 (JP). SEKINE, Shingo [JP/JP]; Remonzu 101, 2–8–15, Atago, Ageo–shi, Saitama 362–0034 (JP). KOBAYASHI, Midori [JP/JP]; Royal Court 306, 3–2–3, Minami–Rinkan, Yamato–shi, Kanagawa 242–0006 (JP).

(74) Agents: AOYAMA, Tamotsu et al.; Aoyama & Partners, IMP Building, 3–7, Shiromi 1–chome, Chuo–ku, Osaka–shi, Osaka 540–0001 (JP).

(81) Designated States: AU, CA, JP, MX, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: HUMAN PROTEINS HAVING TRANSMEMBRANE DOMAINS AND cDNAs ENCODING THESE PROTEINS

(57) Abstract

The invention provides human proteins having transmembrane domains and cDNAs coding for these proteins as well as eukaryotic cells expressing said cDNAs. All of the proteins exist in the cell membrane, so that they are considered to be proteins controlling the proliferation and the differentiation of the cells. Accordingly, the proteins can be employed as pharmaceuticals such as carcinostatic agents relating to the control of the proliferation and the differentiation of the cells or as antigens for preparing antibodies against said proteins. The cDNAs can be utilized as probes for the gene diagnosis and gene sources for the gene therapy. Furthermore, the cDNAs can be utilized for large–scale expression of said proteins. Cells, wherein these membrane protein genes are introduced and membrane proteins are expressed in large amounts, can be utilized for detection of the corresponding ligands, screening of novel low–molecular pharmaceuticals, and so on.

flags p. 7

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CU	Cuba
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakstan
LC	Saint Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	The former Yugoslav Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

DESCRIPTION

Human Proteins Having Transmembrane Domains and DNAs Encoding these Proteins

TECHNICAL FIELD

The present invention relates to human proteins having transmembrane domains and cDNAs coding for these proteins as well as eucaryotic cells expressing said cDNAs. The proteins of the present invention can be employed as pharmaceuticals or as antigens for preparing antibodies against said proteins. The human cDNAs of the present invention can be utilized as probes for the gene diagnosis and gene sources for the gene therapy. Furthermore, the cDNAs can be utilized as gene sources for large-scale production of the proteins encoded by said cDNAs. Cells, wherein these membrane protein genes are introduced and membrane proteins are expressed in large amounts, can be utilized for detection of the corresponding ligands, screening of novel low-molecular pharmaceuticals, and so on.

BACKGROUND ART

Membrane proteins play important roles, as signal receptors, ion channels, transporters, etc. in the material transportation and the information transmission which are mediated by the cell membrane. Examples thereof include receptors for a variety of cytokines, ion channels for the sodium ion, the potassium ion, the chloride ion, etc., transporters for saccharides and amino

acids, and so on, where the genes of many of them have been cloned already.

It has been clarified that abnormalities of these membrane proteins are associated with a number of hitherto-cryptogenic diseases. For instance, a gene of a membrane protein having twelve transmembrane domains was identified as the gene responsible for cystic fibrosis [Rommens, J. M. et al., Science 245: 1059-1065 (1989)]. In addition, it has been clarified that several membrane proteins act as receptors when a virus infects the cells. For instance, HIV-1 is revealed to infect into the cells through mediation of a membrane protein fusin having a membrane protein on the T-cell membrane, a CD-4 antigen, and seven transmembrane domains [Feng, Y. et al., Science 272: 872-877 (1996)]. Therefore, discovery of a new membrane protein is anticipated to lead to elucidation of the causes of many diseases, so that isolation of a new gene coding for the membrane protein has been desired.

Heretofore, owing to difficulty in the purification, many membrane proteins have been isolated by an approach from the gene side. A general method is the so-called expression cloning which comprises transfection of a cDNA library in eucaryotic cells to express cDNAs and then detection of the cells expressing the target membrane protein on the membrane by an immunological technique using an antibody or a physiological technique on the change in the membrane permeability. However, this method is applicable only to cloning of a gene of a membrane protein with a known function.

In general, membrane proteins possess hydrophobic transmembrane domains inside the proteins, wherein, after

synthesis thereof in the ribosome, these domains remain in the phospholipid membrane to be trapped in the membrane. Accordingly, the evidence of the cDNA for encoding the membrane protein is provided by determination of the whole base sequence of a full-length cDNA followed by detection of highly hydrophobic transmembrane domains in the amino acid sequence of the protein encoded by said cDNA.

DISCLOSURE OF INVENTION

The object of the present invention is to provide novel human proteins having transmembrane domains and DNAs coding for said proteins as well as transformation eucaryotic cells that are capable of expressing said cDNAs.

As the result of intensive studies, the present inventors have been successful in cloning of cDNAs coding for proteins having transmembrane domains from the human full-length cDNA bank, thereby completing the present invention. In other words, the present invention provides human proteins having transmembrane domains, namely proteins containing any of the amino acid sequences represented by Sequence Nos. 1 to 10. Moreover, the present invention provides DNAs coding for the above-mentioned proteins, exemplified by cDNAs containing any of the base sequences represented by Sequence Nos. 11 to No. 20, as well as transformation eucaryotic cells that are capable of expressing said cDNAs.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01244.

Figure 2: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01498.

Figure 3: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01565.

Figure 4: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01606.

Figure 5: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01737.

Figure 6: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01962.

Figure 7: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10435.

Figure 8: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10479.

Figure 9: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by

clone HP10481.

Figure 10: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10495.

BEST MODE FOR CARRYING OUT OF THE INVENTION

The proteins of the present invention can be obtained, for example, by a method for isolation from human organs, cell lines, etc., a method for preparation of peptides by the chemical synthesis, or a method for production with the recombinant DNA technology using the DNAs coding for the transmembrane domains of the present invention, wherein the method for obtainment by the recombinant DNA technology is employed preferably. For instance, in vitro expression of the proteins can be achieved by preparation of an RNA by in vitro transcription from a vector having one of cDNAs of the present invention, followed by in vitro translation using this RNA as a template. Also, recombination of the translation region into a suitable expression vector by the method known in the art leads to production of a large amount of the encoded protein by using prokaryotic cells such as *Escherichia coli*, *Bacillus subtilis*, etc., and eucaryotic cells such as yeasts, insect cells, mammalian cells, etc.

In the case in which a protein of the present invention is produced by a microorganism such as *Escherichia coli* etc., a recombinant expression vector bearing the translation region in the cDNA of the present invention is constructed in an expression vector having an origin, a promoter, a ribosome-binding site, a

cDNA-cloning site, a terminator etc., which can be replicated in the microorganism, and, after transformation of the host cells with said expression vector, the thus-obtained transformant is incubated, whereby the protein encoded by said cDNA can be produced on a large scale in the microorganism. In this case, a protein fragment containing an optional region can be obtained by carrying out the expression with inserting an initiation codon and a termination codon in front of and behind an optional translation region. Alternatively, a fusion protein with another protein can be expressed. Only a protein portion coding for said cDNA can be obtained by cleavage of said fusion protein with a suitable protease.

In the case in which one of the proteins of the present invention is produced in eucaryotic cells, the protein of the present invention can be produced as a transmembrane protein on the cell-membrane surface, when the translation region of said cDNA is subjected to recombination to an expression vector for eucaryotic cells that has a promoter, a splicing region, a poly(A) insertion site, etc., followed by introduction into the eucaryotic cells. The expression vector is exemplified by pKA1, Ped6dpc2, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vector, pRS, pYES2, and so on. Examples of eucaryotic cells to be used in general include mammalian culture cells such as simian kidney cells COS7, Chinese hamster ovary cells CHO, etc., budding yeasts, fission yeasts, silkworm cells, *Xenopus laevis* egg cells, and so on, but any eucaryotic cells may be used, provided that they are capable of expressing the present proteins on the membrane surface. The

expression vector can be introduced in the eucaryotic cells by methods known in the art such as the electroporation method, the potassium phosphate method, the liposome method, the DEAE-dextran method, and so on.

After one of the proteins of the present invention is expressed in prokaryotic cells or eucaryotic cells, the objective protein can be isolated from the culture and purified by a combination of separation procedures known in the art. Such examples include treatment with a denaturing agent such as urea or a surface-active agent, sonication, enzymatic digestion, salting-out or solvent precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing, ion-exchange chromatography, hydrophobic chromatography, affinity chromatography, reverse phase chromatography, and so on.

The proteins of the present invention include peptide fragments (more than 5 amino acid residues) containing any partial amino acid sequence in the amino acid sequences represented by Sequence Nos. 1. to 10. These peptide fragments can be utilized as antigens for preparation of antibodies. Hereupon, among the proteins of the present invention, those having the signal sequence are secreted in the form of maturation proteins on the surface of the cells, after the signal sequences are removed. Therefore, these maturation proteins shall come within the scope of the present invention. The N-terminal amino acid sequences of the maturation proteins can be easily identified by using the method for the cleavage-site determination in a signal sequence [Japanese Patent Kokai Publication No. 1996-187100]. Furthermore,

some membrane proteins undergo the processing on the cell surface to be converted to the secretory forms. Such proteins or peptides in the secretory forms shall come within the scope of the present invention. When sugar chain-binding sites are present in the amino acid sequences, expression in appropriate eucaryotic cells affords proteins wherein sugar chains are added. Accordingly, such proteins or peptides wherein sugar chains are added shall come within the scope of the present invention.

The DNAs of the present invention include all DNAs coding for the above-mentioned proteins. Said DNAs can be obtained by using a method by chemical synthesis, a method by cDNA cloning, and so on.

The cDNAs of the present invention can be cloned, for example, from cDNA libraries of the human cell origin. These cDNA are synthesized by using as templates poly(A)$^+$ RNAs extracted from human cells. The human cells may be cells delivered from the human body, for example, by the operation or may be the culture cells. The cDNAs can be synthesized by using any method selected from the Okayama-Berg method [Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-170 (1982)], the Gubler-Hoffman method [Gubler, U. and Hoffman, J. Gene 25: 263-269 (1983)], and so on, but it is preferred to use the capping method [Kato, S. et al., Gene 150: 243-250 (1994)], as exemplified in Examples, in order to obtain a full-length clone in an effective manner.

The primary selection of one of the cDNAs coding for the human proteins having transmembrane domains is carried out by sequencing of a partial base sequence of a cDNA clone selected

at random from cDNA libraries, sequencing of the amino acid sequence encoded by the base sequence, and recognition of the presence or absence of a hydrophobic site in the resulting N-terminal amino acid sequence region. Next, the secondary selection is carried out by determination of the whole sequence by the sequencing and the protein expression by in vitro translation. Ascertainment of cDNAs of the present invention for encoding the proteins having secretory signal sequences is carried out by using the signal sequence detection method [Yokoyama-Kobayashi, M. et al., Gene 163: 193-196 (1995)]. In other words, the ascertainment for a coding portion of an inserted cDNA fragment to function as a signal sequence is provided by fusing a cDNA fragment coding for the N-terminus of the target protein with a cDNA coding for the protease domain of urokinase and then expressing the resulting cDNA in COS7 cells to detect the urokinase activity in the cell culture medium. On the other hand, in the case in which the urokinase activity is not detectable in the cell medium, the N-terminal region is judged to remain in the membrane.

The cDNAs of the present invention are characterized by containing either of the base sequences represented by Sequence Nos. 11 to 20 or the base sequences represented by Sequence Nos. 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39. Table 1 summarizes the clone number (HP number), the cells affording the cDNA, the total base number of the cDNA, and the number of the amino acid residues of the encoded protein, for each of the cDNAs.

Table 1

Sequence No.	HP No.	Cell	Number of bases	Number of amino acids
1, 11, 21	HP01244	Stomach Cancer	979	123
2, 12, 22	HP01498	Stomach Cancer	1279	220
3, 13, 23	HP01565	Stomach Cancer	835	81
4, 14, 24	HP01606	Stomach Cancer	1256	301
5, 15, 25	HP01737	Stomach Cancer	1305	383
6, 16, 26	HP01962	Liver	899	199
7, 17, 27	HP10435	Stomach Cancer	905	229
8, 18, 28	HP10479	PMA—U937	841	178
9, 19, 29	HP10481	PMA—U937	1451	443
10, 20, 30	HP10495	Stomach Cancer	886	130

Hereupon, the same clones as the cDNAs of the present invention can be easily obtained by screening of the cDNA libraries constructed from the human cell lines and human tissues utilized in the present invention by the use of an oligonucleotide probe synthesized on the basis of the cDNA base sequence described in any of Sequence Nos. 11 to 21, 23, 25, 27, 29, 31, 35, 37 and 39.

In general, the polymorphism due to the individual difference is frequently observed in human genes. Accordingly, any cDNA that is subjected to insertion or deletion of one or plural nucleotides and/or substitution with other nucleotides in Sequence Nos. 11 to 21, 23, 25, 27, 29, 31, 35, 37 and 39 shall come within the scope of the present invention.

In a similar manner, any protein that is formed by these modifications comprising insertion or deletion of one or plural amino acids and/or substitution with other amino acids shall come

within the scope of the present invention, as far as the protein possesses the activity of any protein having the amino acid sequences represented by Sequence Nos. 1 to 10.

The cDNAs of the present invention include cDNA fragments (more than 10 bp) containing any partial base sequence in the base sequences represented by Sequence Nos. 11 to 20 or in the base sequences represented by Sequence Nos. 21, 23, 25, 27, 29, 30, 31, 33, 35 and 39. Also, DNA fragments consisting of a sense chain and an anti-sense chain shall come within this scope. These DNA fragments can be utilized as the probes for the gene diagnosis.

In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as

molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodiesusing DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which

the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a

particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in

Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6-Nordan, R. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett,

F., Giannotti, J., Clark, S.C. and Turner, K. J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting

the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial orfungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may

be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a

monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development

of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune

responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the commoncold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of

the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class IIα chain protein and an MHC class IIβ chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an

antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J.J. and Brunswick, M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental

Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other

cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may

be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part

of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating

hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian

cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology,

Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result,such a protein is expected to be useful in treatment of various coagulation disorders (includinghereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods

175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of ytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may

inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders)

and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

Examples

The present invention is embodied in more detail by the following examples, but this embodiment is not intended to restrict the present invention. The basic operations and the enzyme reactions with regard to the DNA recombination are carried out according to the literature ["Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Laboratory, 1989]. Unless otherwise stated, restrictive enzymes and a variety of modification enzymes to be used were those available from TAKARA SHUZO. The manufacturer's instructions were used for the buffer compositions as well as for the reaction conditions, in each of the enzyme reactions. The cDNA synthesis was carried out according to the literature [Kato, S. et al., Gene 150: 243-250 (1994)].

(1) Preparation of Poly(A)$^+$ RNA

The histiocyte lymphoma cell line U937 (ATCC CRL 1593)

stimulated by phorbol ester, tissues of stomach cancer delivered by the operation, and the liver were used for human cells to extract mRNAs. The cell line was incubated by a conventional procedure.

After about 1 g of the human cells was homogenized in 20 ml of a 5.5 M guanidinium thiocyanate solution, a total mRNA was prepared according to the literature [Okayama, H. et al., "Method in Enzymology", Vol. 164, Academic Press, 1987]. This was subjected to chromatography on oligo(dT)-cellulose column washed with a 20 mM Tris-hydrochloride buffer solution (pH 7.6), 0.5 M NaCl, and 1 mM EDTA to obtain a poly(A)$^+$ RNA according to the above-described literature.

(2) Construction of cDNA Library

Ten micrograms of the above-mentioned poly(A)$^+$ RNA were dissolved in a 100 mM Tris-hydrochloride buffer solution (pH 8), one unit of an RNase-free, bacterial alkaline phosphatase was added, and the reaction was run at 37℃ for one hour. After the reaction solution was subjected to phenol extraction, followed by ethanol precipitation, the resulting pellet was dissolved in a solution containing 50 mM sodium acetate (pH 6), 1 mM EDTA, 0.1% 2-mercaptoethanol, and 0.01% Triton X-100. Thereto was added one unit of a tobacco-origin acid pyrophosphatase (Epicentre Technologies) and a total 100 μl volume of the resulting mixture was reacted at 37℃ for one hour. After the reaction solution was subjected to phenol extraction, followed by ethanol precipitation, the resulting pellet was dissolved in water to obtain a solution of a decapped poly(A)$^+$ RNA.

The decapped poly(A)$^+$ RNA and 3 nmol of a chimeric DNA-

RNA oligonucleotide (5'-dG-dG-dG-dG-dA-dA-dT-dT-dC-dG-dA-G-G-A-3') were dissolved in a solution containing 50 mM Tris-hydrochloride buffer solution (pH 7.5), 0.5 mM ATP, 5 mM $MgCl_2$, 10 mM 2-mercaptoethanol, and 25% polyethylene glycol, whereto was added 50 units of T4RNA ligase and a total 30 µl volume of the resulting mixture was reacted at 20℃ for 12 hours. After the reaction solution was subjected to phenol extraction, followed by ethanol precipitation, the resulting pellet was dissolved in water to obtain a chimeric-oligo-capped poly(A)$^+$ RNA.

After digestion of vector pKA1 (Japanese Patent Kokai Publication No. 1992-117292) developed by the present inventors with KpnI, about 60 dT tails were added using a terminal transferase. A vector primer to be used below was prepared by digestion of this product with EcoRV to remove a dT tail at one side.

After 6 µg of the previously-prepared chimeric-oligo-capped poly(A)$^+$ RNA was annealed with 1.2 µg of the vector primer, the resulting product was dissolved in a solution containing 50 mM Tris-hydrochloride buffer solution (pH 8.3), 75 mM KCl, 3 mM $MgCl_2$, 10 mM dithiothreitol, and 1.25 mM dNTP (dATP + dCTP + dGTP + dTTP), 200 units of a reverse transcriptase (GIBCO-BRL) were added, and the reaction in a total 20 µl volume was run at 42℃ for one hour. After the reaction solution was subjected to phenol extraction, followed by ethanol precipitation, the resulting pellet was dissolved in a solution containing 50 mM Tris-hydrochloride buffer solution (pH 7.5), 100 mM NaCl, 10 mM $MgCl_2$, and 1 mM dithiothreitol. Thereto were added 100 units of EcoRI and a total 20 µl volume of the resulting mixture was reacted at

37℃ for one hour. After the reaction solution was subjected to phenol extraction, followed by ethanol precipitation, the resulting pellet was dissolved in a solution containing 20 mM Tris-hydrochloride buffer solution (pH 7.5), 100 mM KCl, 4 mM $MgCl_2$, 10 mM $(NH_4)_2SO_4$, and 50 μg/ml of the bovine serum albumin. Thereto were added 60 units of an *Escherichia coli* DNA ligase and the resulting mixture was reacted at 16℃ for 16 hours. To the reaction solution were added 2 μl of 2 mM dNTP, 4 units of *Escherichia coli* DNA polymerase I, and 0.1 unit of *Escherichia coli* RNase H and the resulting mixture was reacted at 12℃ for one hour and then at 22℃ for one hour.

Next, the cDNA-synthesis reaction solution was used for transformation of *Escherichia coli* DH12S (GIBCO-BRL). The transformation was carried out by the electroporation method. A portion of the transformant was sprayed on the 2xYT agar culture medium containing 100 μg/ml ampicillin and the mixture was incubated at 37℃ overnight. A colony formed on the agar medium was picked up at random and inoculated on 2 ml of the 2xYT culture medium containing 100 μg/ml ampicillin. After incubation at 37℃ overnight, the culture mixture was centrifuged to separate the mycelia, from which a plasmid DNA was prepared by the alkaline lysis method. The plasmid DNA was subjected to double digestion with EcoRI and NotI, followed by 0.8% agarose gel electrophoresis, to determine the size of the cDNA insert. Furthermore, using the thus-obtained plasmid as a template, the sequence reaction was carried out by using an M13 universal primer labeled with a fluorescent dye and a Taq polymerase (a kit of Applied Biosystems)

and then the product was examined with a fluorescent DNA sequencer (Applied Biosystems) to determine an about 400-bp base sequence at the 5'-terminus of the cDNA. The sequence data were filed as the homo/protein cDNA bank database.

(3) Selection of cDNAs Encoding Proteins Having Transmembrane Domains

A base sequence registered in the homo/protein cDNA bank was converted to three frames of amino acid sequences and the presence or absence of an open reading frame (ORF) beginning from the initiation codon was examined. Then, the selection was made for the presence of a signal sequence that is characteristic to a secretory protein at the N-terminus of the portion encoded by the ORF. These clones were sequenced from the both 5' and 3' directions by the use of the deletion method using exonuclease III to determine the whole base sequence. The hydrophobicity/hydrophilicity profiles were obtained for proteins encoded by the ORF by the Kyte-Doolittle method [Kyte, J. & Doolittle, R. F., J. Mol. Biol. 157: 105-132 (1982)] to examine the presence or absence of a hydrophobic region. In the case in which there is a hydrophobic region of a putative transmembrane domain in the amino acid sequence of an encoded protein, this protein was judged as a membrane protein.

(4) Functional Verification of Secretory Signal Sequence or Transmembrane Domains

It was verified by the method described in the literature [Yokoyama-Kobayashi, M. et al., Gene 163: 193-196 (1995)] that the N-terminal hydrophobic region in the secretory protein clone

candidate obtained in the above-mentioned steps functions as a secretory signal sequence. First, the plasmid containing the target cDNA was cleaved at an appropriate restriction enzyme site existing at the downstream of the portion expected for encoding the secretory signal sequence. In the case in which this restriction site was a protruding terminus, the site was blunt-ended by the Klenow treatment or treatment with the mung-bean nuclease. Digestion with HindIII was further carried out and a DNA fragment containing the SV40 promoter and a cDNA encoding the secretory signal sequence at the downstream of the promoter was separated by agarose gel electrophoresis. The resulting fragment was inserted between HindIII in pSSD3 (DDBJ/EMBL/GenBank Registration No. AB007632) and a restriction enzyme site selected so as to match with the urokinase-coding frame, thereby constructing a vector expressing a fusion protein of the secretory signal sequence of the target cDNA and the urokinase protease domain.

After *Escherichia coli* (host: JM109) bearing the fusion-protein expression vector was incubated at 37℃ for 2 hours in 2 ml of the 2xYT culture medium containing 100 μg/ml of ampicillin, the helper phage M13KO7 (50 μl) was added and the incubation was continued at 37 ℃ overnight. A supernatant separated by centrifugation underwent precipitation with polyethylene glycol to obtain single-stranded phage particles. These particles were suspended in 100 μl of 1 mM Tris-0.1 mM EDTA, pH 8 (TE). Also, there were used as controls suspensions of single-stranded phage particles prepared in the same manner from

pSSD3 and from the vector pKA1-UPA containing a full-length cDNA of urokinase [Yokoyama-Kobayashi, M. et al., Gene 163: 193-196 (1995)].

The culture cells originating from the simian kidney, COS7, were incubated at 37℃ in the presence of 5% CO_2 in the Dulbecco's modified Eagle's culture medium (DMEM) containing 10% fetal calf albumin. Into a 6-well plate (Nunc Inc., 3 cm in the well diameter) were inoculated 1×10^5 COS7 cells and incubation was carried out at 37℃ for 22 hours in the presence of 5% CO_2. After the culture medium was removed, the cell surface was washed with a phosphate buffer solution and then washed again with DMEM containing 50 mM Tris-hydrochloric acid (pH 7.5) (TDMEM). To the resulting cells was added a suspension of 1 µl of the single-stranded phage suspension, 0.6 ml of the DMEM culture medium, and 3 µl of TRANSFECTAM™ (IBF Inc.) and the resulting mixture was incubated at 37℃ for 3 hours in the presence of 5% CO_2. After the sample solution was removed, the cell surface was washed with TDMEM, 2 ml per well of DMEM containing 10% fetal calf albumin was added, and the incubation was carried out at 37℃ for 2 days in the presence of 5% CO_2.

To 10 ml of 50 mM phosphate buffer solution (pH 7.4) containing 2% bovine fibrinogen (Miles Inc.), 0.5% agarose, and 1 mM calcium chloride were added 10 units of human thrombin (Mochida Pharmaceutical Co., Ltd.) and the resulting mixture was solidified in a plate of 9 cm in diameter to prepare a fibrin plate. Ten microliters of the culture supernatant of the tansfected COS7 cells were spotted on the fibrin plate, which was incubated at

37℃ for 15 hours. In the case in which a clear circle appears on the fibrin plate, it is judged that the cDNA fragment codes for the amino acid sequence functioning as a secretory signal sequence. On the other hand, in case in which a clear circle is not formed, the cells were washed well, then the fibrin sheet was placed on the cells, and incubation was carried out at 37℃ for 15 hours. In case in which a clear portion is formed on the fibrin sheet, it indicates that the urokinase activity was expressed on the cell surface. In other words, the cDNA fragment is judged to code for the transmembrane domains.

(5) Protein Synthesis by In Vitro Translation

The plasmid vector bearing the cDNA of the present invention was used for in vitro transcription/translation with a T_NT rabbit reticulocyte lysate kit (Promega). In this case, [^{35}S]methionine was added to label the expression product with a radioisotope. Each of the reactions was carried out according to the protocols attached to the kit. Two micrograms of the plasmid was reacted at 30℃ for 90 minutes in a total 25 μl volume of the reaction solution containing 12.5 μl of T_NT rabbit reticulocyte lysate, 0.5 μl of a buffer solution (attached to kit), 2 μl of an amino acid mixture (methionine-free), 2 μl of [^{35}S]methionine (Amersham) (0.37 MBq/μl), 0.5 μl of T7RNA polymerase, and 20 U of RNasin. To 3 μl of the resulting reaction solution was added 2 μl of the SDS sampling buffer (125 mM Tris-hydrochloric acid buffer, pH 6.8, 120 mM 2-mercaptoethanol, 2% SDS solution, 0.025% bromophenol blue, and 20% glycerol) and the resulting mixture was heated at 95℃ for 3 minutes and then subjected to SDS-polyacrylamide gel

electrophoresis. The molecular weight of the translation product was determined by carrying out the autoradiograph.

(6) Expression by COS7

Escherichia coli bearing the expression vector of the protein of the present invention was infected with helper phage M13KO7 and single-stranded phage particles were obtained by the above-mentioned procedure. The thus-obtained phage was used for introducing each expression vector in the culture cells originating from the simian kidney, COS7. After incubation at 37℃ for 2 days in the presence of 5% CO_2, the incubation was continued for one hour in the culture medium containing [^{35}S]cystine or [^{35}S]methionine. Collection and dissolution of the cells, followed by subjecting to SDS-PAGE, allowed to observe the presence of a band corresponding to the expression product of each protein, on the membrane fraction which did not exist in the COS7 cells. For instance, the molecular weights of HP01498, HP01565, HP01737, HP010435 and HP010495 were respectively 20 kDa, 13 kDa, 52 kDa, 33 kDa and 20 kDa.

(7) Clone Examples

<HP01244> (Sequence Nos. 1, 11, and 21)

Determination of the whole base sequence of the cDNA insert of clone HP01244 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 15-bp 5'-nontranslation region, a 372-bp ORF, and a 592-bp 3'-nontranslation region. The ORF codes for a protein consisting of 123 amino acid residues and there existed a signal-like sequence at the N-terminus and one transmembrane domain at the C-terminal.

Figure 1 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 14 kDa that was almost consistent with the molecular weight of 12,911 predicted from the ORF.

The search of the protein data base by using the amino acid sequence of the present protein revealed that the protein was analogous to the chicken stem cell antigen 2 (GenBank Accession No. L34554). Table 2 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the chicken stem cell antigen 2 (GG). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 33.9% in the entire region.

Table 2

```
HS MKAVLLALLMAGLALQPGTALLCYSCKAQVSNEDCLQVKNCTQLGEQCWTA--RIRAVGL
   *** *.*.* * * .... .*.*.**... ** .**   .*.. .*.* *.    .   *
GG MKAFLFAVLAAVLCVERAHTLICFSCSDASSNWACLTPVKCAENEEHCVTTYVGVGIGGK
HS LT-VISKGCSLNCVDDSQDYYVGKKNITCCDTDLCNASGAHALQPAAAILAL--LPALGL
    .  ******  * ... .  ..  .. ***. *** **. ..... *.***  * ..
GG SGQSISKGCSPVCPSAGINLGIAAASVYCCDSFLCNISGSSSVKASYAVLALGILVSFVY
HS LLWGPGQL
   .*..
GG VLRARE
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of

sequences that possessed a homology of 90% or more (for example, Accession No. AA476643) in EST, but many sequences were not distinct and the same ORF as that in the present cDNA was not found.

<HP01498> (Sequence Nos. 2, 12, and 23)

Determination of the whole base sequence of the cDNA insert of clone HP01498 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 227-bp 5'-nontranslation region, a 663-bp ORF, and a 389-bp 3'-nontranslation region. The ORF codes for a protein consisting of 220 amino acid residues and there existed four transmembrane domains. Figure 2 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 22 kDa that was almost consistent with the molecular weight of 23,318 predicted from the ORF.

The search of the protein data base by using the amino acid sequence of the present protein revealed that the protein was analogous to the rat protein RVP1 (NBRF Accession No. A39484). Table 3 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the rat protein RVP1(RN). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 81.8% in the entire region. Hereupon, the rat protein had a sequence longer by 60 amino acid residues at the C-terminal side.

Table 3

```
HS MSMGLEITGTALAVLGWLGTIVCCALPMWRVSAFIGSNIITSQNIWEGLWMNCVVQSTGQ
   ***.******.******* ******************.***.* .******** ******
RN MSMSLEITGTSLAVLGWLCTIVCCALPMWRVSAFIGSSIITAQITWEGLWMNC-VQSTGQ
HS MQCKVYDSLLALPQDLQAARALIVVAILLAAFGLLVALVGAQCTNCVQDDTAKAKITIVA
   ****.********************.***********************.**********
RN MQCKMYDSLLALPQDLQAARALIVVSILLAAFGLLVALVGAQCTNCVQDETAKAKITIVA
HS GVLFLLAALLTLVPVSWSANTIIRDFYNPVVPEAQKREMGAGLYVGWAAAALQLLGGALL
   ********.********************.**********.*******************
RN GVLFLLAAVLTLVPVSWSANTIIRDFYNPLVPEAQKREMGTGLYVGWAAAALQLLGGALL
HS CCSCPPREKKYTATKVVYSAPRSTGPGASLGTGYDRKDYV
   ******** **..**..**********.. **.****
RN CCSCPPRE-KYAPTKILYSAPRSTGPGTGTGTAYDRKTTSERPGARTPHHHHYQPSMYPT
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more (for example, Accession No. H72008) in EST, but many sequences were not distinct and the same ORF as that in the present cDNA was not found.

The rat protein RVP1 is one of membrane proteins which are induced by androgen withdrawal and apoptosis in the rat ventral prostate [Briehl, M. M. et al., Mol. Endocrinol. 5: 1381-1388 (1991)]. Accordingly, the present protein is considered to play an important role in the signal transduction that is associated with apoptosis.

<HP01565> (Sequence Nos. 3, 13, and 25)

Determination of the whole base sequence of the cDNA insert of clone HP01565 obtained from cDNA libraries of human stomach

cancer revealed the structure consisting of a 62-bp 5'-nontranslation region, a 246-bp ORF, and a 527-bp 3'-nontranslation region. The ORF codes for a protein consisting of 81 amino acid residues and there existed two transmembrane domains. Figure 3 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 10 kDa that was almost consistent with the molecular weight of 9,374 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein has revealed the presence of sequences that were analogous to the nematode putative protein F49C12.13 (GenBank Accession No. Z68227). Table 4 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the nematode putative protein F49C12.13 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 47.4% in the entire region.

Table 4

```
HS        MAYHGLTVPLIVMSVFWGFVGFLVPWFIPKGPNRGVIITMLVTCSVCCYLFWL
              *. .**. .*.**...**  **..*******.*  *..  .***..**.
CE MCNFSYFQLQMGILIPLVSVSAFWAIIGFGGPWIVPKGPNRGIIQLMIIMTAVCCWMFWI
HS IAILAQLNPLFGPQLKNETIWYLKYHWP
   ...* *****.***..  .**....  .*
CE MVFLHQLNPLIGPQINVKTIRWISEKWGDAPNVINN
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more (for example, Accession No. N57319) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP01606> (Sequence Nos. 4, 14, and 27)

Determination of the whole base sequence of the cDNA insert of clone HP01606 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 124-bp 5′-nontranslation region, a 906-bp ORF, and a 226-bp 3′-nontranslation region. The ORF codes for a protein consisting of 301 amino acid residues and there existed seven transmembrane domains. Figure 4 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 31 kDa that was almost consistent with the molecular weight of 32,594 predicted from the ORF.

The search of the protein data base using the amino acid

sequence of the present protein has revealed the presence of sequences that were analogous to the nematode putative protein F13H11.9 (GenBank Accession No. AF003389). Table 5 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the nematode putative protein F13H11.9 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 45.1% in the region of 195 amino acid residues at the C-terminal side.

Table 5

```
HS MLALRVARGSWGALRGAAWAPGTRPSKRRACWALLPPVPCCLGCLAERWRLRPAALGLRL

CE                                                     MIVTSMFR
HS PGIGQRNHCSGAGKAAPRPAAGAGAAAEAPGGQWGPASTPSLYENPWTIPNMLSMTRIGL
                                   *..... *. . **** .. .**.
CE GIACRCELQLLLTPRRMLRNFSSLEQKQSPKIESLPPEERGKYKVA-TIPNAICTARIAA
HS APVLGYLIIEEDFNIALGVFALAGLTDLLDGFIARNWANQRSALGSALDPLADKILISIL
   .*..***.....*. *. .*..** *********** ..*.* ***.***.***.***..
CE TPLIGYLVVQHNFTPAFVLFTVAGATDLLDGFIARNVPGQKSLLGSVLDPVADKLLISTM
HS YVSLTYADLIPVPLTYMIISRDVMLIAAVFYVRYRTLPTPRTLAKYFNPCYATARLKPTF
   ....***.***.*** ..* **. **.. ** **.....* .*...***  .. .. **.
CE FITMTYAGLIPLPLTSVVILRDICLIGGGFYKRYQVMSPPYSLSRFFNPQVSSMQVVPTM
HS ISKVNTAVQLILVAASLAAPVFNYADSIY--LQILWCFTAFTTAASAYSYYHYGRKTVQV
   .**.**..*..*** **..***.....     .   * *.*.***  *.  *
CE MSKINTVLQITLVALSLSSPVFDFSTGANDVIVGLGCITGFTTIYSGLQYASGKAIKKI
```

Furthermore, the search of the GenBank using the base

sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more (for example, Accession No. C16798) in EST, but many sequences were not distinct and the same ORF as that in the present cDNA was not found.

<HP01737> (Sequence Nos. 5, 15, and 29)

Determination of the whole base sequence of the cDNA insert of clone HP01737 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 21-bp 5'-nontranslation region, a 1152-bp ORF, and a 132-bp 3'-nontranslation region. The ORF codes for a protein consisting of 383 amino acid residues and there existed two transmembrane domains. Figure 5 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 45 kDa that was almost consistent with the molecular weight of 43,222 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein has revealed the presence of sequences that were analogous to the nematode putative protein K09E9.2 (GenBank Accession No. Z79602). Table 6 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the nematode putative protein K09E9.2 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 42.2% in the region of 195 amino acid residues at

the C-terminal side.

Table 6

```
HS MEALGKLKQFDAYPKTLEDFRVKTCGGATVTIVSGLLMLLLFLSELQYYLTTEVHPELYV
   *. *.**.****.*...****** .*. **..... ..**.. * . .*.***  .*.*
CE MSLLWSLKHFDAYRKPMDDFRVKTLSGGLVTLIATIAIVLLIVLETKQFLSTEVLEHLFV
HS D-KSRGDKLKINIDVLFPHMPCAYLSIDAMDVAGEQQLDVEHNLFKQRLDKDGIPVSSEA
   * ........*..*. *...**.....*.***..*.* ........ *** .*  .*..*
CE DSTTSDERVHIEFDITFTKLPCNFITVDVMDVSSEAQENINDDIYRLRLDPEGRNISESA
HS ERHELGKVEVTVFDPDSLDPDRCESCYGAEAEDIKCCNTCEDVREAYRRRGWAFKNPDTI
   .. *... ...* ..* ..  .*.*****.*..* *****.**..**  .**.  * ...
CE QKIEINQNKTSVETTDVIQEVKCGSCYGAAADGI-CCNTCDDVKSAYAVKGWQV-NIEEV
HS EQCRREGFSQKMQEQKNEGCQVYGFLEVNKVAGNFHFAPGKSFQQSHVHVHDLQSFGLDN
   ***... . ....*.*****.*** ..*.*******.***.. *. . *****....  .
CE EQCKNDKWVKEFNEHKNEGCRVYGTVKVAKVAGNFHLAPGDPHQAMRSHVHDLHNLDPVK
HS INMTHYIQHLSFGEDYPGIVNPLDHTNVTAPQASMMFQYFVKVVPTVYMKVDGEVLRTNQ
   .. .* ..*.***...**    *** .  *. ....*.**.****** *  .** * ...*
CE FDASHTVNHVSFGKSFPGKNYPLDGKVNTDNRGGIMYQYYVKVVPTRYDYLDGRVDQSHQ
HS FSVTRHEKVANGLLGDQGLPGVFVLYELSPMMVKLTEKHRSFTHFLTGVCAIIGGMFTVA
   **** *.*  .  . . **** *. **.**.**. .* ..**. **...***.**.*..*
CE FSVTTHKK--DLGFRQSGLPGFFLQYEFSPLMVQYEEFRQSFASFLVSLCAIVGGVFAMA
HS GLIDSLIYHSARAIQKKIDLGKTT
     *.*  ****.* ....*. ** *
CE QLVDITIYHSSRYMKSRIAGGKLT
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more (for example, Accession No. H42261) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP01962> (Sequence Nos. 6, 16, and 31)

Determination of the whole base sequence of the cDNA insert of clone HP01962 obtained from cDNA libraries of human liver revealed the structure consisting of a 73-bp 5'-nontranslation region, a 600-bp ORF, and a 226-bp 3'-nontranslation region. The ORF codes for a protein consisting of 199 amino acid residues and there existed at least three transmembrane domains. Figure 6 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 21 kDa that was almost consistent with the molecular weight of 22,134 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein has revealed the presence of sequences that were analogous to a rat phosphatidylethanolamine N-methyltransferase (SWISS-PROT Accession No. Q08388). Table 7 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the rat phosphatidylethanolamine N-methyltransferase (RN). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 80.8% in the entire region.

Table 7

```
HS MTRLLGYVDPLDPSFVAAVITITFNPLYWNVVARWEHKTRKLSRAFGSPYLACYSLSVTI
     ..******* .*******.**.****.********..******************.  .*
RN  SWLLGYVDPTEPSFVAAVLTIVFNPLFWNVVARWEQRTRKLSRAFGSPYLACYSLGSII
HS LLLNFLRSHCFTQAMLSQPRMESLDTPAAYSLGLALLGLGVVLVLSSFFALGFAGTFLGD
   ****.**********.***.**.**...  * ******* *.*.*****.****.******
RN LLLNILRSHCFTQAMMSQPKMEGLDSHTIYFLGLALLGWGLVFVLSSFYALGFTGTFLGD
HS YFGILKEARVTVFPFNILDNPMYWGSTANYLGWAIMHASPTGLLLTVLVALTYIVALLYE
   *******.***.***..*****************.****************.*.****.*
RN YFGILKESRVTTFPFSVLDNPMYWGSTANYLGWALMHASPTGLLLTVLVALVYVVALLFE
HS EPFTAEIYRQKASGSHKRS
   *********.**.   ****
RN EPFTAEIYRRKATRLHKRS
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more and contained an initiation codon (for example, Accession No. H83024) in EST, but many sequences were not distinct and the same ORF as that in the present cDNA was not found.

The rat phosphatidylethanolamine N-methyltransferase is a membrane protein which is associated with the biosynthesis of phosphatidylethanolamine [Cui, Z. et al., J. Biol. Chem. 268: 16655-16663 (1993)]. The present protein is considered to be a human homologue of the phosphatidylethanolamine N-methyltransferase and is utilized for the diagnosis and treatment of diseases that are associated with abnormalities of this enzyme.

<HP10435> (Sequence Nos. 7, 17, and 23)

Determination of the whole base sequence of the cDNA insert of clone HP10435 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of an 8-bp 5'-nontranslation region, a 690-bp ORF, and a 207-bp 3'-nontranslation region. The ORF codes for a protein consisting of 229 amino acid residues and there existed one transmembrane domain each at the N-terminus and at the C-terminus. Figure 7 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. Introduction of an expression vector, wherein the HindIII-BalI fragment containing a cDNA portion coding for the N-terminal 109 amino acid residues of the present protein was inserted into the HindIII-EcoRV site of pSSD3, into the COS7 cells revealed the urokinase activity on the cell surface to indicate that the present protein remains in the membrane. In vitro translation resulted in formation of a translation product of 24 kDa that was almost consistent with the molecular weight of 24,688 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein has not revealed the presence of any known protein having an analogy. Also, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more and contained an initiation codon (for example, Accession No. H87685) in EST, but many sequences were not distinct and the same ORF as that in the present cDNA was not found.

<HP10479> (Sequence Nos. 8, 18, and 35)

Determination of the whole base sequence of the cDNA insert of clone HP10479 obtained from cDNA libraries of the human lymphoma U937 revealed the structure consisting of a 38-bp 5'-nontranslation region, a 537-bp ORF, and a 266-bp 3'-nontranslation region. The ORF codes for a protein consisting of 178 amino acid residues and there existed a signal-like sequence at the N-terminus and one transmembrane domain at the C-terminus. Figure 8 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. Introduction of an expression vector, wherein the HindIII-BanII (blunt-ended by treatment with T4DNA polymerase) fragment containing a cDNA portion coding for the N-terminal 45 amino acid residues of the present protein was inserted into the HindIII-SmaI site of pSSD3, into the COS7 cells revealed the urokinase activity in the culture medium to indicate that the present protein is the type-I membrane protein. In vitro translation resulted in formation of a translation product of 33 kDa that was larger than the molecular weight of 19,453 predicted from the ORF. Application of the (-3,-1) rule, a method for predicting the cleavage site in the secretory signal sequence, allows to expect that the maturation protein starts from glutamine at position 22.

The search of the protein data base using the amino acid sequence of the present protein has revealed the presence of sequences that were analogous to the mouse ion channel homologue RIC (GenBank Accession No. U72680). Table 8 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the mouse ion channel homologue RIC (MM).

Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 48.1% in the entire region.

Table 8

```
HS MSPSGRLCLLTIVGLILPTRGQTLKDTTSSSSADSTIMDIQVPTRAPDAVYTELQPTSPT
   ** *.********.****.**** *..**  .** *   ...   ...**..  ...*.*.  .
MM MSLSSRLCLLTIVALILPSRGQTPKKPTSIFTADQTSATTRDNVPDPDQTSPGVQTTPLI
HS PTWPADETPQ--PQTQTQQLEG-TDGPLVTDPETHKSTKAAHPTDDTTTLSERPSPSTDV
    *.  .....*  .**.****.   ...   *.**..*.*.* .  *    ...   *.  ***..
MM WTREEATGSQTAAQTETQQLTKMATSNPVSDPGPHTSSKKGTP---AVSRIEPLSPSKNF
HS QTDPQTLKPSGFHEDDPFFYDEHTLRKRGLLVAAVLFITGIIILTSGKCRQLSRLCRNHC
    .  .  .  .* .  .*..**.**.  ******************************..* *.
MM MPPSYIEHPLDSNENNPFYYDDTTLRKRGLLVAAVLFITGIIILTSGKCRQLSQFCLNRH
HS R
   *
MM R
```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more (for example, Accession No. AA296696) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

The mouse ion channel homologue RIC is one of proteins which are induced on introduction of E2a-Pbx1 oncoprotein into the

NIH3T3 fibroblast cells and has been considered to play an important role in the cell cycle and proliferation [Fu, X. et al., Mol. Cell. Biol. 17: 1503-1512 (1997)].

<HP10481> (Sequence Nos. 9, 19, and 37)

Determination of the whole base sequence of the cDNA insert of clone HP10481 obtained from cDNA libraries of the human lymphoma U937 revealed the structure consisting of a 104-bp 5'-nontranslation region, a 1332-bp ORF, and a 15-bp 3'-nontranslation region. The ORF codes for a protein consisting of 443 amino acid residues and there existed one transmembrane domain at the N-terminus. Figure 9 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. Introduction of an expression vector, wherein the HindIII-PvuII fragment containing a cDNA portion coding for the N-terminal 148 amino acid residues of the present protein was inserted into the HindIII-EcoRV site of pSSD3, into the COS7 cells revealed the urokinase activity on the cell surface to indicate that the present protein is the type-II membrane protein. In vitro translation resulted in formation of a translation product of 51 kDa that was almost consistent with the molecular weight of 51,145 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein has not revealed the presence of any known protein having an analogy. Also, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more (for example, Accession No. AA354554) in EST, but any of the

sequences was shorter than the present cDNAs and was not found to contain the initiation codon.

<HP10495> (Sequence Nos. 10, 20, and 39)

Determination of the whole base sequence of the cDNA insert of clone HP10495 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 62-bp 5'-nontranslation region, a 393-bp ORF, and a 431-bp 3'-nontranslation region. The ORF codes for a protein consisting of 130 amino acid residues and there existed two transmembrane domains. Figure 10 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 25 kDa that was larger than the molecular weight of 14,964 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein has not revealed the presence of any known protein having an analogy. Also, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more (for example, Accession No. AA431001) in EST, but each of them was shorter than the present cDNA and was not found to contain the initiation codon.

INDUSTRIAL APPLICABILITY

The present invention provides human proteins having transmembrane domains and cDNAs coding for these proteins as well as eucaryotic cells expressing said cDNAs. All of the proteins

of the present invention exist in the cell membrane, so that they are considered to be proteins controlling the proliferation and the differentiation of the cells. Accordingly, the proteins of the present invention can be employed as pharmaceuticals such as carcinostatic agents relating to the control of the proliferation and the differentiation of the cells or as antigens for preparing antibodies against said proteins. The cDNAs of the present invention can be utilized as probes for the gene diagnosis and gene sources for the gene therapy. Furthermore, the cDNAs can be utilized for large-scale expression of said proteins. Cells, wherein these membrane protein genes are introduced and membrane proteins are expressed in large amounts, can be utilized for detection of the corresponding ligands, screening of novel low-molecular pharmaceuticals, and so on.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for

identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, Trends Pharmacol. Sci. 15(7): 250-254; Lavarosky et al., 1997, Biochem. Mol. Med. 62(1): 11-22; and Hampel, 1998, Prog. Nucleic Acid Res. Mol. Biol. 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through

deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, Bioessays 14(9): 629-633; Zwaal et al., 1993, Proc. Natl. Acad. Sci. USA 90(16): 7431-7435; Clark et al., 1994, Proc. Natl. Acad. Sci. USA 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour et al., 1988, Nature 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614, 396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s).

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-

occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Table 9

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp)‡	Hybridization Temperature and Buffer†	Wash Temperature and Buffer†
A	DNA : DNA	≥50	65℃; 1×SSC -or- 42℃: 1×SSC.50% formamide	65℃; 0.3×SSC
B	DNA : DNA	<50	T_B*; 1×SSC	T_B*; 1×SSC
C	DNA : RNA	≥50	67℃: 1×SSC -or- 45℃: 1×SSC.50% formamide	67℃: 0.3×SSC
D	DNA : RNA	<50	T_D*: 1×SSC	T_D*: 1×SSC
E	RNA : RNA	≥50	70℃: 1×SSC -or- 50℃: 1×SSC.50% formamide	70℃: 0.3×SSC
F	RNA : RNA	<50	T_F*: 1×SSC	T_F*: 1×SSC
G	DNA : DNA	≥50	65℃: 4×SSC -or- 42℃: 4×SSC.50% formamide	65℃: 1×SSC
H	DNA : DNA	<50	T_H*: 4×SSC	T_H*: 4×SSC
I	DNA : RNA	≥50	67℃: 4×SSC -or- 45℃: 4×SSC.50% formamide	67℃: 1×SSC
J	DNA : RNA	<50	T_J*; 4×SSC	T_J*: 4×SSC
K	RNA : RNA	≥50	70℃: 4×SSC -or- 50℃: 4×SSC.50% formamide	67℃: 1×SSC
L	RNA : RNA	<50	T_L*; 2×SSC	T_L*; 2×SSC
M	DNA : DNA	≥50	50℃; 4×SSC -or- 40℃: 6×SSC.50% formamide	50℃: 2×SSC
N	DNA : DNA	<50	T_N*; 6×SSC	T_N*; 6×SSC
O	DNA : RNA	≥50	55℃: 4×SSC -or- 42℃: 6×SSC.50% formamide	55℃: 2×SSC
P	DNA : RNA	<50	T_P*; 6×SSC	T_P*; 6×SSC
Q	RNA : RNA	≥50	60℃: 4×SSC -or- 45℃: 6×SSC.50% formamide	60℃: 2×SSC
R	RNA : RNA	<50	T_R*: 4×SSC	T_R*: 4×SSC

‡ : The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence. the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized. the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

† : SSPE (1×SSPE is 0.15M NaCl. 10mM NaH_2PO_4. and 1.25mM EDTA, pH7.4) can be substituted for SSC (1×SSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R : The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10℃ less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length. T_m(℃)=2(#of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(℃)=81.5 + 16.6($\log_{10}[Na^+]$) + 0.41 (%G+C) - (600/N), where N is the number of bases in the hybrid. and $[Na^+]$ is the concentration of sodium ions in the hybridization buffer ($[Na^+]$ for 1×SSC=0.165M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

CLAIMS

1. A protein comprising any of the amino acid sequences represented by Sequence Nos. 1 to 10.

2. A DNA coding for the protein according to Claim 1.

3. A cDNA comprising any of the base sequences represented by Sequence Nos. 11 to 20.

4. The cDNA according to Claim 3 comprising any of the base sequences represented by Sequence Nos. 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39.

5. A vector capable of expressing the DNA or cDNA according to any of Claims 2 to 4 in in vitro translation or an eucaryotic cell.

6. A transformation eucaryotic cell capable of expressing the DNA or cDNA according to any of Claim 2 to 4 to produce the protein according to Claim 1.

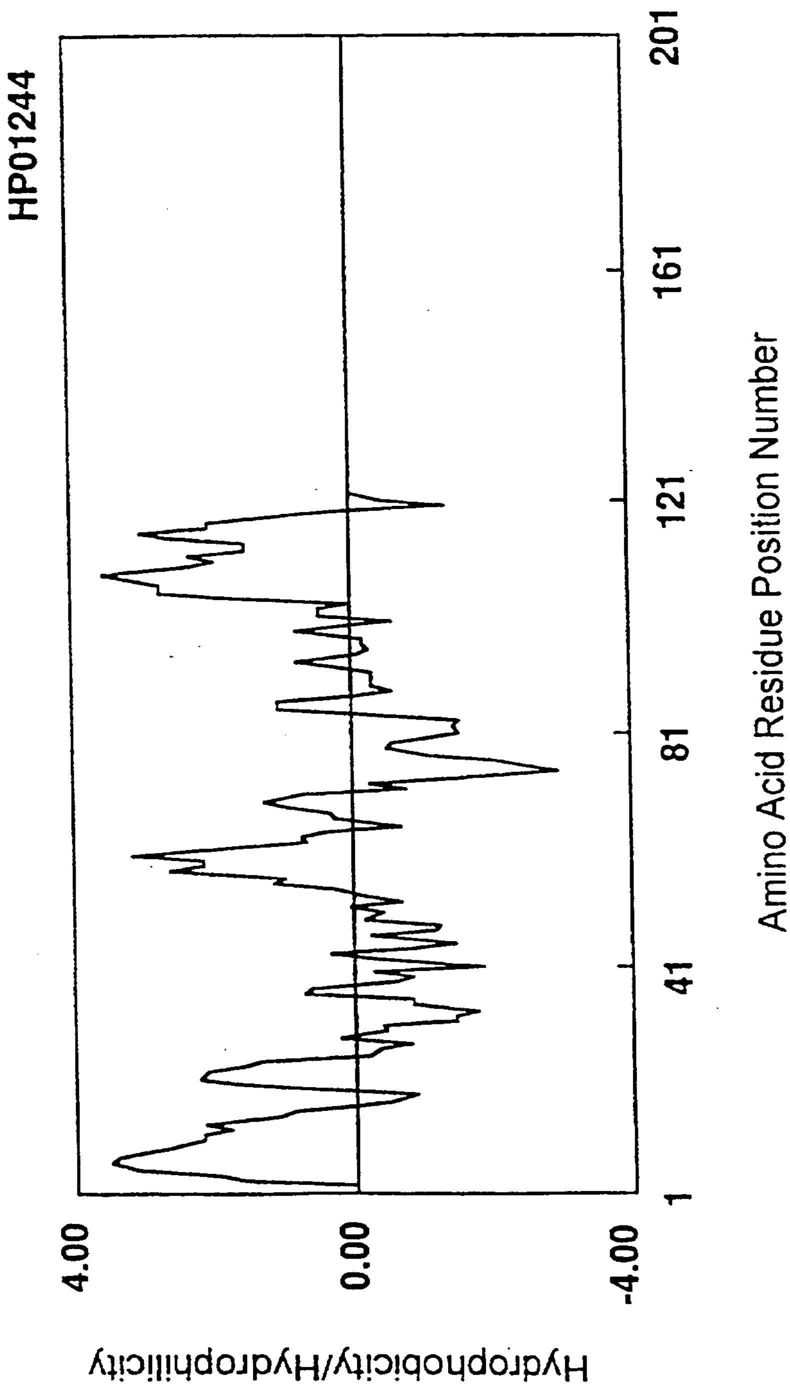
HP01244
4.00
0.00
-4.00
Hydrophobicity/Hydrophilicity
1
41
81
121
161
201
Amino Acid Residue Position Number

Fig. 1

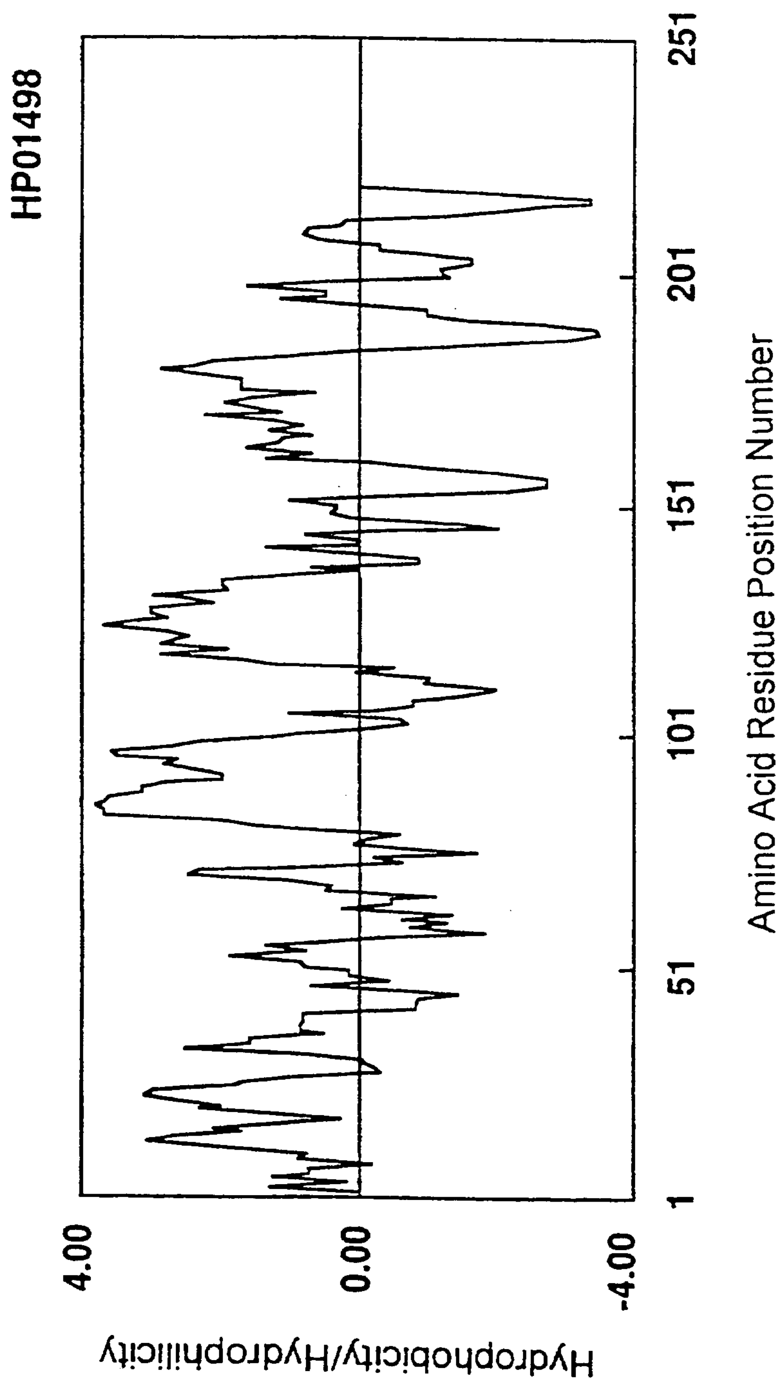
HP01498
4.00
0.00
-4.00
Hydrophobicity/Hydrophilicity
1
51
101
151
201
251
Amino Acid Residue Position Number

Fig. 2

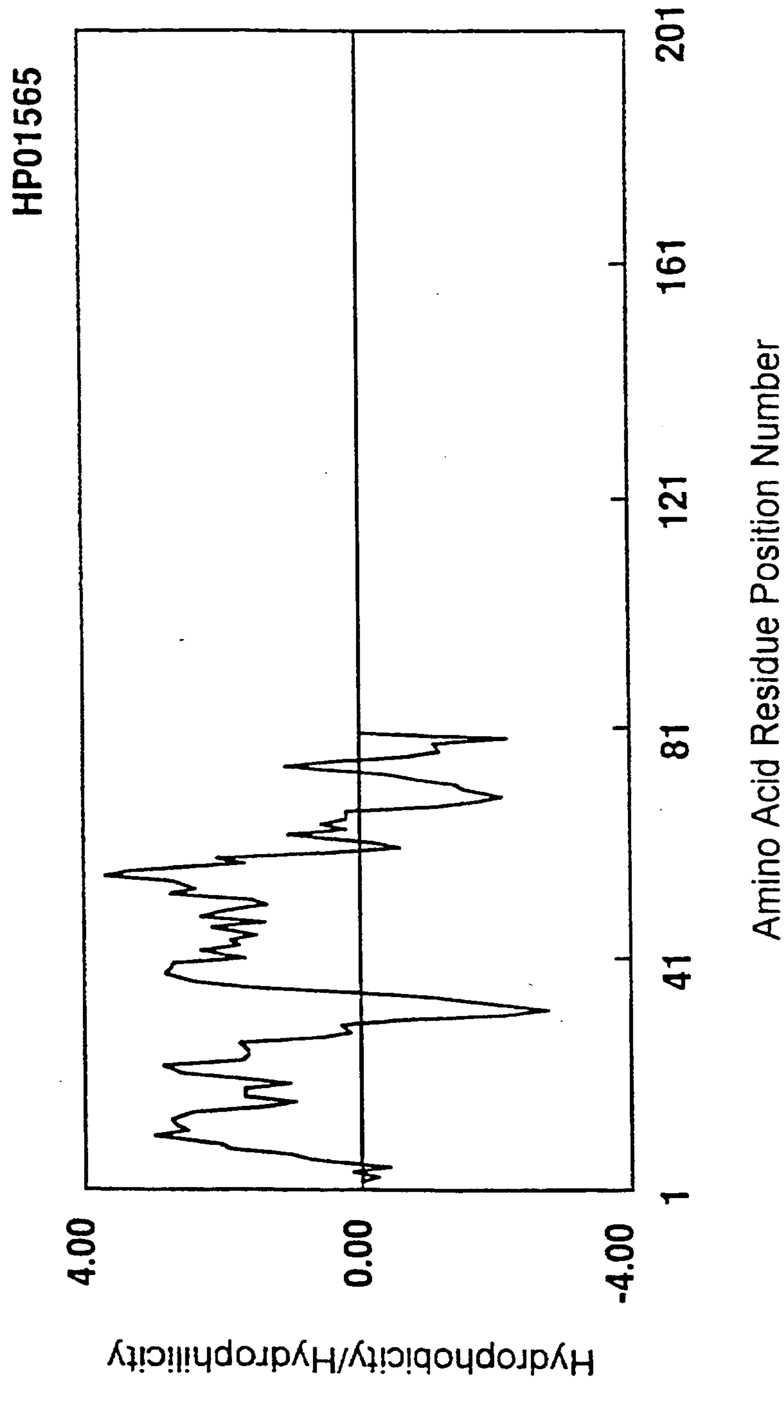
HP01565
4.00
0.00
-4.00
Hydrophobicity/Hydrophilicity
1
41
81
121
161
201
Amino Acid Residue Position Number

Fig. 3

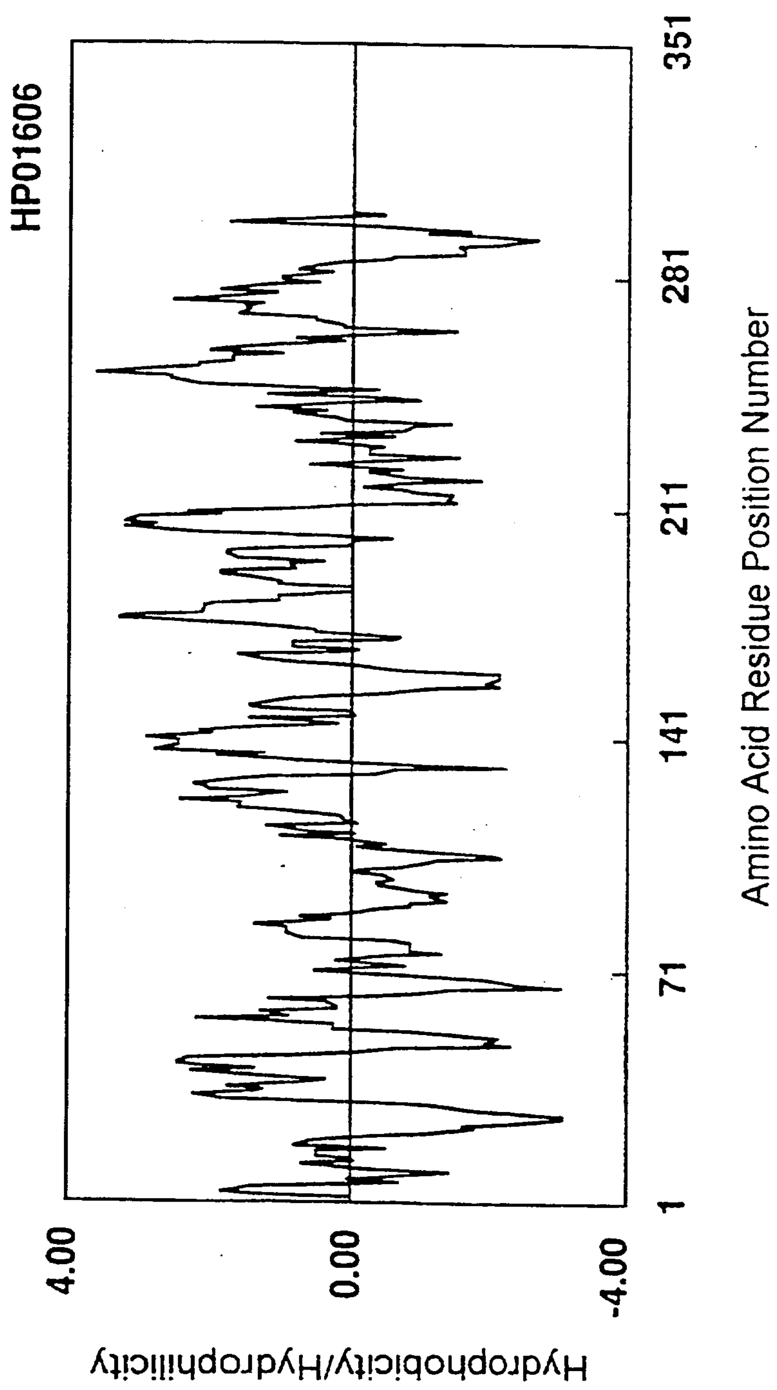
HP01606
4.00
0.00
-4.00
1
71
141
211
281
351
Amino Acid Residue Position Number
Hydrophobicity/Hydrophilicity

Fig. 4

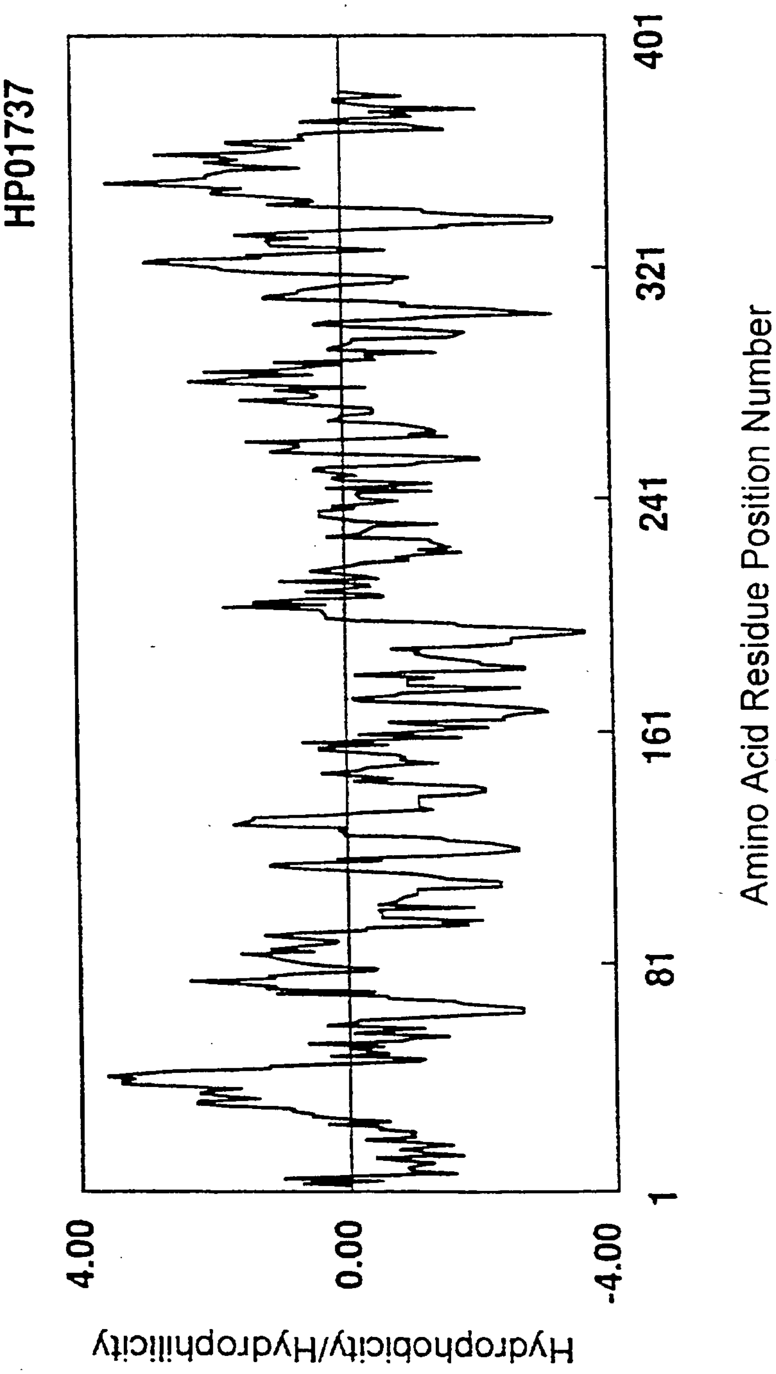
HP01737
4.00
0.00
-4.00
Hydrophobicity/Hydrophilicity
1
81
161
241
321
401
Amino Acid Residue Position Number

Fig. 5

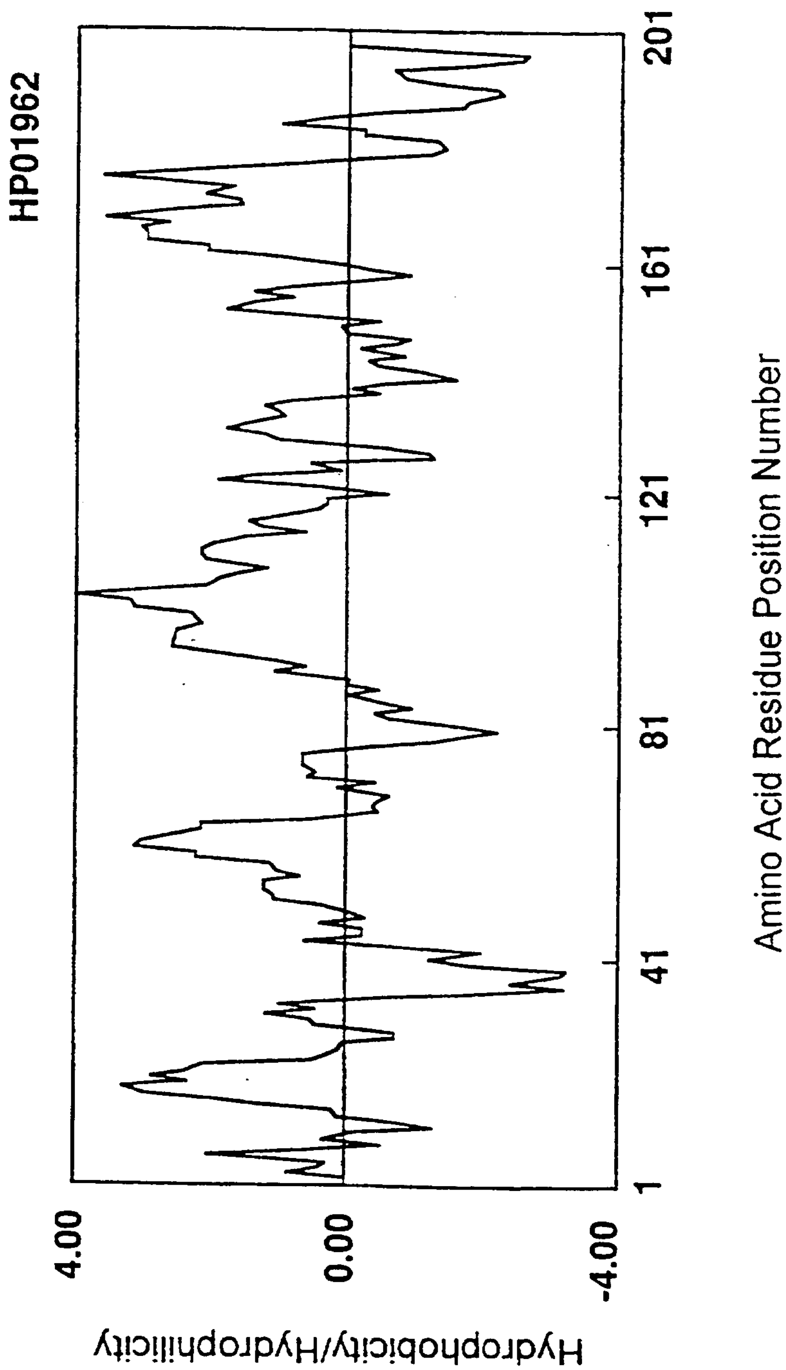
HP01962
4.00
0.00
-4.00
Hydrophobicity/Hydrophilicity
1
41
81
121
161
201
Amino Acid Residue Position Number

Fig. 6

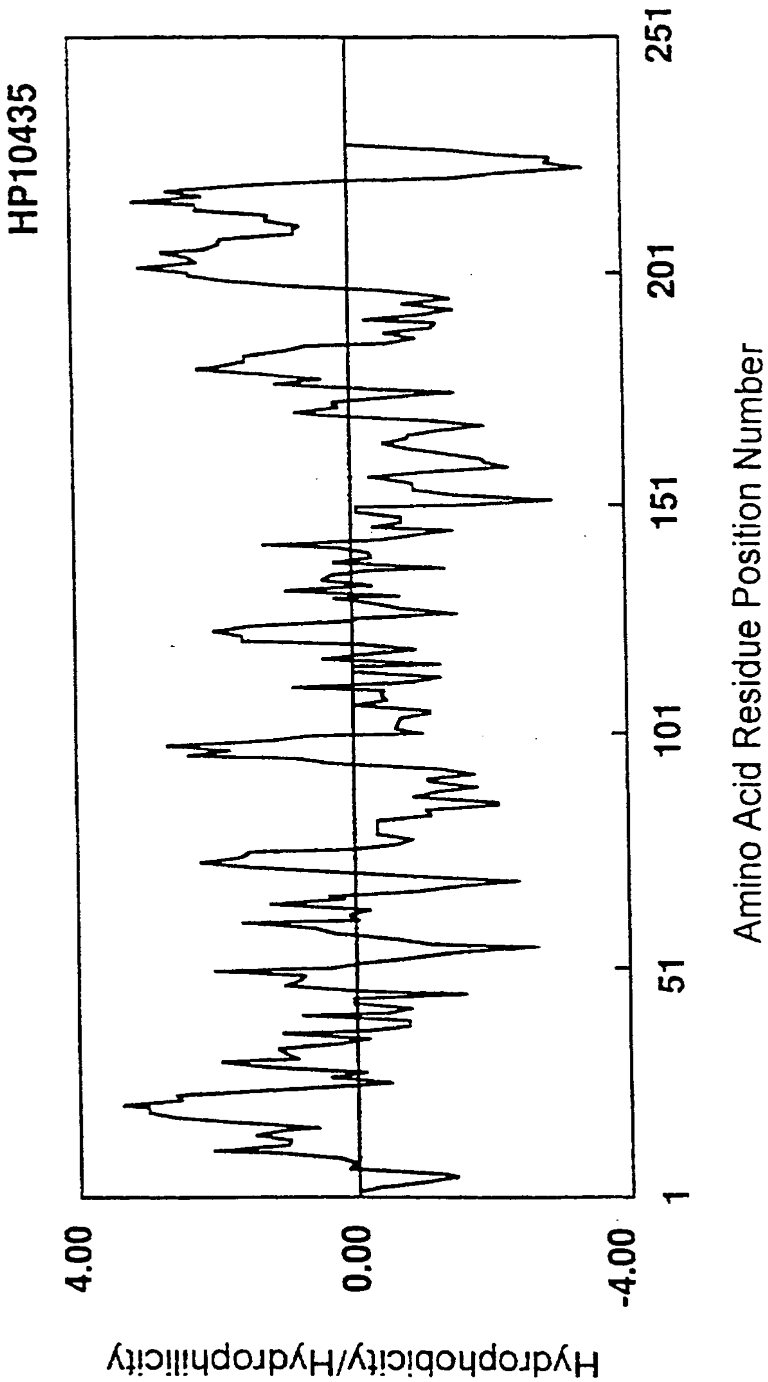
HP10435
Hydrophobicity/Hydrophilicity
4.00
0.00
-4.00
1
51
101
151
201
251
Amino Acid Residue Position Number

Fig. 7

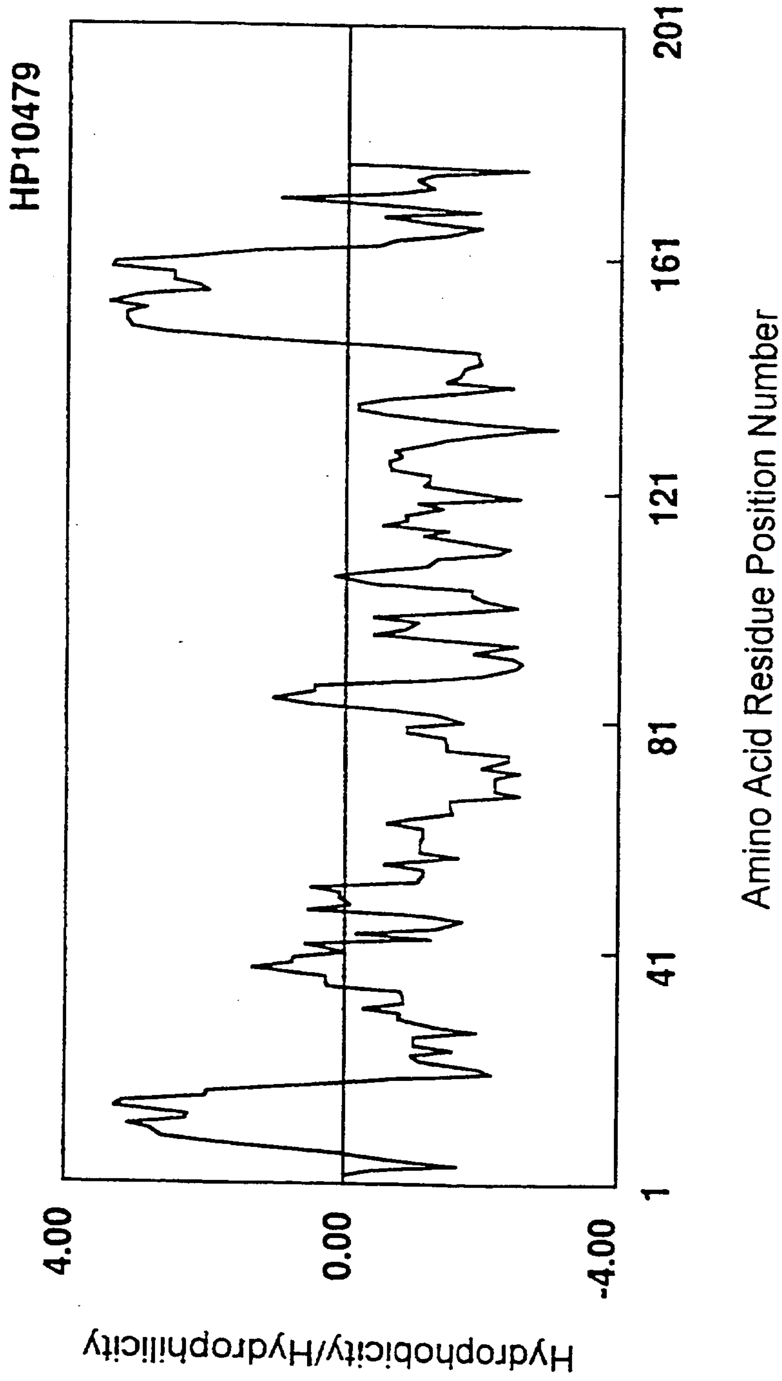
HP10479
4.00
0.00
-4.00
Hydrophobicity/Hydrophilicity
1
41
81
121
161
201
Amino Acid Residue Position Number

Fig. 8

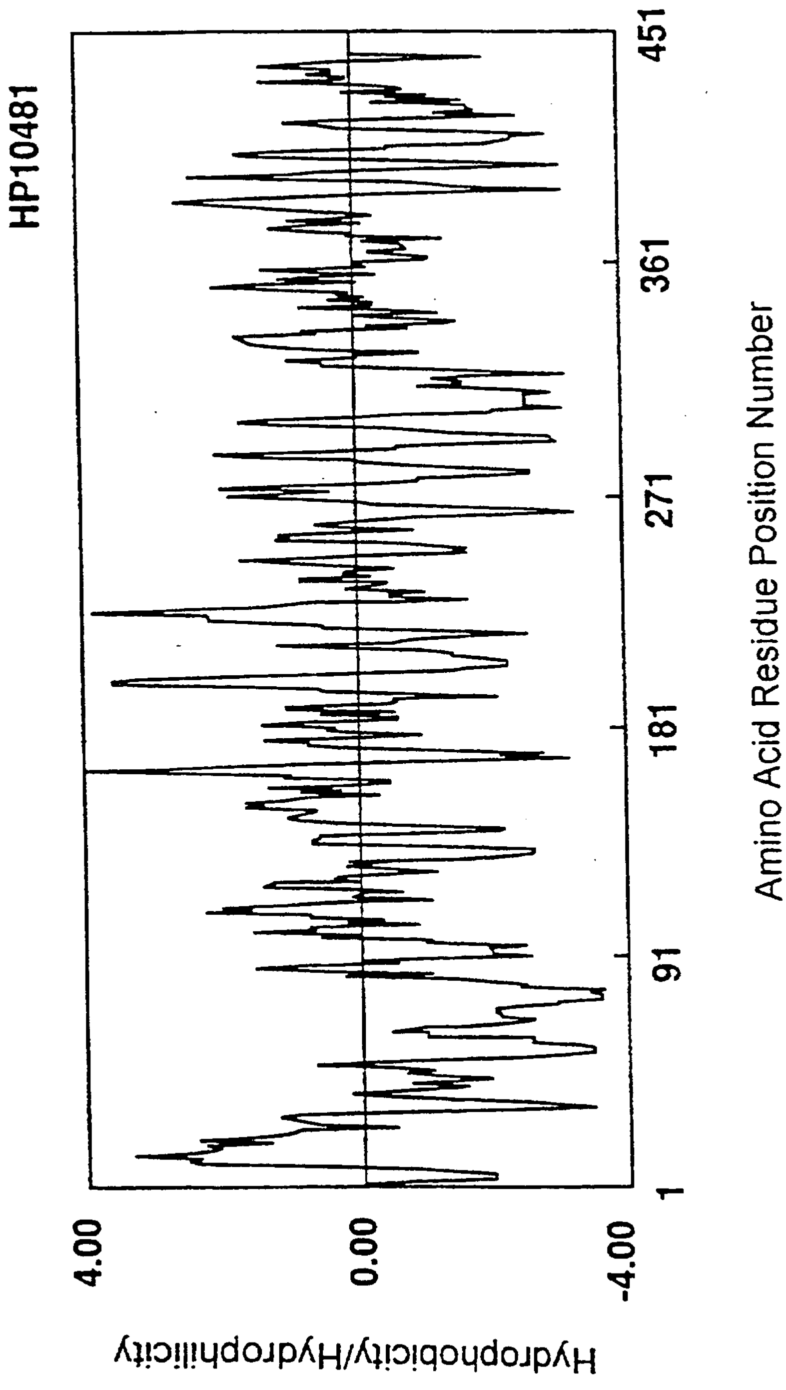
HP10481
4.00
0.00
-4.00
Hydrophobicity/Hydrophilicity
1
91
181
271
361
451
Amino Acid Residue Position Number

Fig. 9

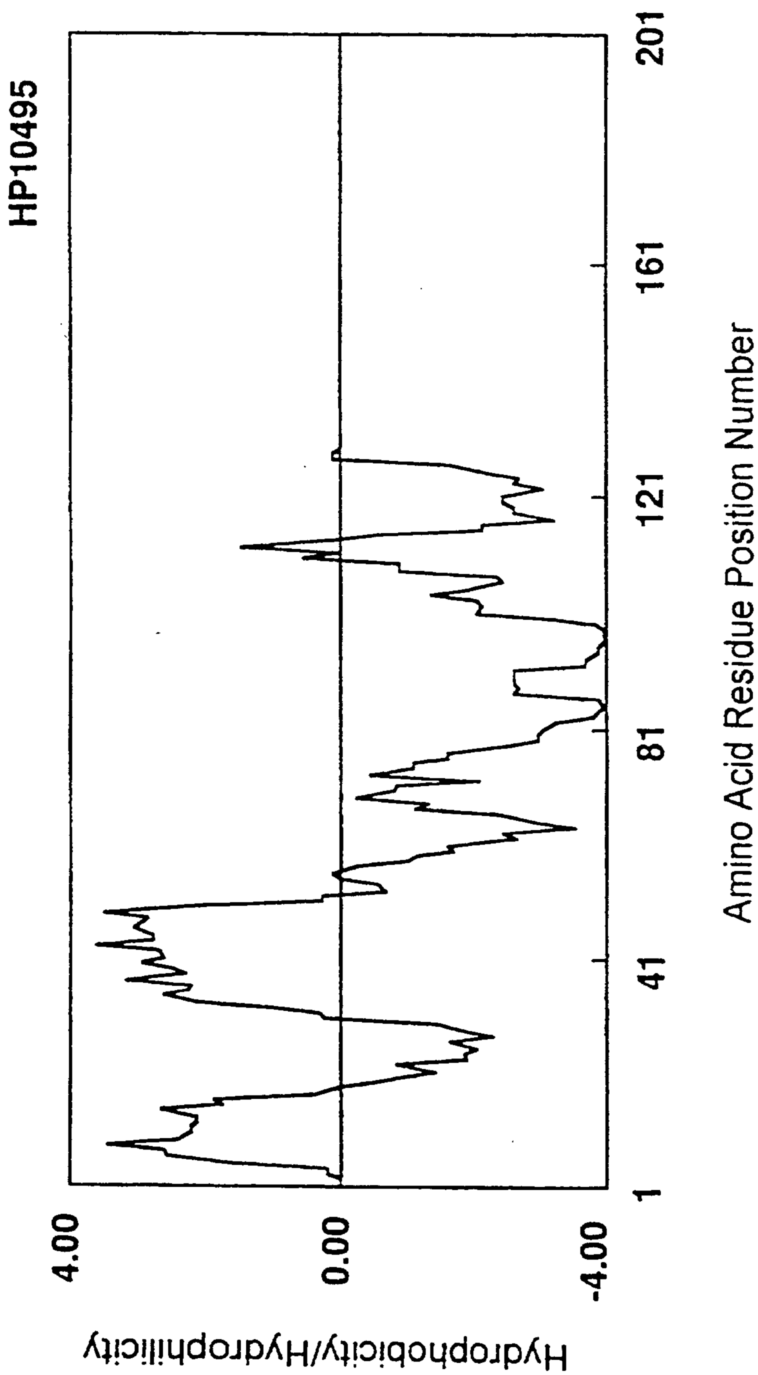
HP10495
4.00
0.00
-4.00
1
41
81
121
161
201
Amino Acid Residue Position Number
Hydrophobicity/Hydrophilicity

Fig. 10

Sequence Listing

<110> Sagami Chemical Research Center

<120>

<130> 660856

<140>

<141>

<150> Japan 9-276271

<151> 1997-10-08

<160> 40

<170> Windows 95 (Word 98)

<210> 1

<211> 123

<212> PRT

<213> Homo sapiens

<400> 1

Met Lys Ala Val Leu Leu Ala Leu Leu Met Ala Gly Leu Ala Leu Gln
1   5   10   15

Pro Gly Thr Ala Leu Leu Cys Tyr Ser Cys Lys Ala Gln Val Ser Asn
            20   25   30

Glu Asp Cys Leu Gln Val Lys Asn Cys Thr Gln Leu Gly Glu Gln Cys

35 40 45

Trp Thr Ala Arg Ile Arg Ala Val Gly Leu Leu Thr Val Ile Ser Lys

50 55 60

Gly Cys Ser Leu Asn Cys Val Asp Asp Ser Gln Asp Tyr Tyr Val Gly

65 70 75 80

Lys Lys Asn Ile Thr Cys Cys Asp Thr Asp Leu Cys Asn Ala Ser Gly

85 90 95

Ala His Ala Leu Gln Pro Ala Ala Ala Ile Leu Ala Leu Leu Pro Ala

100 105 110

Leu Gly Leu Leu Leu Trp Gly Pro Gly Gln Leu

115 120

<210> 2

<211> 220

<212> PRT

<213> Homo sapiens

<400> 2

Met Ser Met Gly Leu Glu Ile Thr Gly Thr Ala Leu Ala Val Leu Gly

1 5 10 15

Trp Leu Gly Thr Ile Val Cys Cys Ala Leu Pro Met Trp Arg Val Ser

20 25 30

Ala Phe Ile Gly Ser Asn Ile Ile Thr Ser Gln Asn Ile Trp Glu Gly

35 40 45

Leu Trp Met Asn Cys Val Val Gln Ser Thr Gly Gln Met Gln Cys Lys

50 55 60

Val Tyr Asp Ser Leu Leu Ala Leu Pro Gln Asp Leu Gln Ala Ala Arg

65 70 75 80

Ala Leu Ile Val Val Ala Ile Leu Leu Ala Ala Phe Gly Leu Leu Val

85 90 95

Ala Leu Val Gly Ala Gln Cys Thr Asn Cys Val Gln Asp Asp Thr Ala

100 105 110

Lys Ala Lys Ile Thr Ile Val Ala Gly Val Leu Phe Leu Leu Ala Ala

115 120 125

Leu Leu Thr Leu Val Pro Val Ser Trp Ser Ala Asn Thr Ile Ile Arg

130 135 140

Asp Phe Tyr Asn Pro Val Val Pro Glu Ala Gln Lys Arg Glu Met Gly

145 150 155 160

Ala Gly Leu Tyr Val Gly Trp Ala Ala Ala Ala Leu Gln Leu Leu Gly

165 170 175

Gly Ala Leu Leu Cys Cys Ser Cys Pro Pro Arg Glu Lys Lys Tyr Thr

180 185 190

Ala Thr Lys Val Val Tyr Ser Ala Pro Arg Ser Thr Gly Pro Gly Ala

195 200 205

Ser Leu Gly Thr Gly Tyr Asp Arg Lys Asp Tyr Val

210 215 220

<210> 3

<211> 81

<212> PRT

<213> Homo sapiens

<400> 3

Met Ala Tyr His Gly Leu Thr Val Pro Leu Ile Val Met Ser Val Phe
1 5 10 15

Trp Gly Phe Val Gly Phe Leu Val Pro Trp Phe Ile Pro Lys Gly Pro
20 25 30

Asn Arg Gly Val Ile Ile Thr Met Leu Val Thr Cys Ser Val Cys Cys
35 40 45

Tyr Leu Phe Trp Leu Ile Ala Ile Leu Ala Gln Leu Asn Pro Leu Phe
50 55 60

Gly Pro Gln Leu Lys Asn Glu Thr Ile Trp Tyr Leu Lys Tyr His Trp
65 70 75 80

Pro

<210> 4

<211> 301

<212> PRT

<213> Homo sapiens

<400> 4

Met Leu Ala Leu Arg Val Ala Arg Gly Ser Trp Gly Ala Leu Arg Gly
1 5 10 15

Ala Ala Trp Ala Pro Gly Thr Arg Pro Ser Lys Arg Arg Ala Cys Trp
20 25 30

Ala Leu Leu Pro Pro Val Pro Cys Cys Leu Gly Cys Leu Ala Glu Arg
35 40 45

Trp Arg Leu Arg Pro Ala Ala Leu Gly Leu Arg Leu Pro Gly Ile Gly

50 55 60

Gln Arg Asn His Cys Ser Gly Ala Gly Lys Ala Ala Pro Arg Pro Ala

65 70 75 80

Ala Gly Ala Gly Ala Ala Ala Glu Ala Pro Gly Gly Gln Trp Gly Pro

85 90 95

Ala Ser Thr Pro Ser Leu Tyr Glu Asn Pro Trp Thr Ile Pro Asn Met

100 105 110

Leu Ser Met Thr Arg Ile Gly Leu Ala Pro Val Leu Gly Tyr Leu Ile

115 120 125

Ile Glu Glu Asp Phe Asn Ile Ala Leu Gly Val Phe Ala Leu Ala Gly

130 135 140

Leu Thr Asp Leu Leu Asp Gly Phe Ile Ala Arg Asn Trp Ala Asn Gln

145 150 155 160

Arg Ser Ala Leu Gly Ser Ala Leu Asp Pro Leu Ala Asp Lys Ile Leu

165 170 175

Ile Ser Ile Leu Tyr Val Ser Leu Thr Tyr Ala Asp Leu Ile Pro Val

180 185 190

Pro Leu Thr Tyr Met Ile Ile Ser Arg Asp Val Met Leu Ile Ala Ala

195 200 205

Val Phe Tyr Val Arg Tyr Arg Thr Leu Pro Thr Pro Arg Thr Leu Ala

210 215 220

Lys Tyr Phe Asn Pro Cys Tyr Ala Thr Ala Arg Leu Lys Pro Thr Phe

225 230 235 240

Ile Ser Lys Val Asn Thr Ala Val Gln Leu Ile Leu Val Ala Ala Ser

245 250 255

Leu Ala Ala Pro Val Phe Asn Tyr Ala Asp Ser Ile Tyr Leu Gln Ile

260 265 270

Leu Trp Cys Phe Thr Ala Phe Thr Thr Ala Ala Ser Ala Tyr Ser Tyr

275 280 285

Tyr His Tyr Gly Arg Lys Thr Val Gln Val Ile Lys Asp

290 295 300

<210> 5

<211> 383

<212> PRT

<213> Homo sapiens

<400> 5

Met Glu Ala Leu Gly Lys Leu Lys Gln Phe Asp Ala Tyr Pro Lys Thr

1 5 10 15

Leu Glu Asp Phe Arg Val Lys Thr Cys Gly Gly Ala Thr Val Thr Ile

20 25 30

Val Ser Gly Leu Leu Met Leu Leu Leu Phe Leu Ser Glu Leu Gln Tyr

35 40 45

Tyr Leu Thr Thr Glu Val His Pro Glu Leu Tyr Val Asp Lys Ser Arg

50 55 60

Gly Asp Lys Leu Lys Ile Asn Ile Asp Val Leu Phe Pro His Met Pro

65 70 75 80

Cys Ala Tyr Leu Ser Ile Asp Ala Met Asp Val Ala Gly Glu Gln Gln

85 90 95

Leu Asp Val Glu His Asn Leu Phe Lys Gln Arg Leu Asp Lys Asp Gly

100 105 110

Ile Pro Val Ser Ser Glu Ala Glu Arg His Glu Leu Gly Lys Val Glu
115 120 125
Val Thr Val Phe Asp Pro Asp Ser Leu Asp Pro Asp Arg Cys Glu Ser
130 135 140
Cys Tyr Gly Ala Glu Ala Glu Asp Ile Lys Cys Cys Asn Thr Cys Glu
145 150 155 160
Asp Val Arg Glu Ala Tyr Arg Arg Arg Gly Trp Ala Phe Lys Asn Pro
165 170 175
Asp Thr Ile Glu Gln Cys Arg Arg Glu Gly Phe Ser Gln Lys Met Gln
180 185 190
Glu Gln Lys Asn Glu Gly Cys Gln Val Tyr Gly Phe Leu Glu Val Asn
195 200 205
Lys Val Ala Gly Asn Phe His Phe Ala Pro Gly Lys Ser Phe Gln Gln
210 215 220
Ser His Val His Val His Asp Leu Gln Ser Phe Gly Leu Asp Asn Ile
225 230 235 240
Asn Met Thr His Tyr Ile Gln His Leu Ser Phe Gly Glu Asp Tyr Pro
245 250 255
Gly Ile Val Asn Pro Leu Asp His Thr Asn Val Thr Ala Pro Gln Ala
260 265 270
Ser Met Met Phe Gln Tyr Phe Val Lys Val Val Pro Thr Val Tyr Met
275 280 285
Lys Val Asp Gly Glu Val Leu Arg Thr Asn Gln Phe Ser Val Thr Arg
290 295 300
His Glu Lys Val Ala Asn Gly Leu Leu Gly Asp Gln Gly Leu Pro Gly
305 310 315 320
Val Phe Val Leu Tyr Glu Leu Ser Pro Met Met Val Lys Leu Thr Glu

325 330 335

Lys His Arg Ser Phe Thr His Phe Leu Thr Gly Val Cys Ala Ile Ile

340 345 350

Gly Gly Met Phe Thr Val Ala Gly Leu Ile Asp Ser Leu Ile Tyr His

355 360 365

Ser Ala Arg Ala Ile Gln Lys Lys Ile Asp Leu Gly Lys Thr Thr

370 375 380

<210> 6

<211> 199

<212> PRT

<213> Homo sapiens

<400> 6

Met Thr Arg Leu Leu Gly Tyr Val Asp Pro Leu Asp Pro Ser Phe Val

1 5 10 15

Ala Ala Val Ile Thr Ile Thr Phe Asn Pro Leu Tyr Trp Asn Val Val

20 25 30

Ala Arg Trp Glu His Lys Thr Arg Lys Leu Ser Arg Ala Phe Gly Ser

35 40 45

Pro Tyr Leu Ala Cys Tyr Ser Leu Ser Val Thr Ile Leu Leu Leu Asn

50 55 60

Phe Leu Arg Ser His Cys Phe Thr Gln Ala Met Leu Ser Gln Pro Arg

65 70 75 80

Met Glu Ser Leu Asp Thr Pro Ala Ala Tyr Ser Leu Gly Leu Ala Leu

85 90 95

Leu Gly Leu Gly Val Val Leu Val Leu Ser Ser Phe Phe Ala Leu Gly

100 105 110

Phe Ala Gly Thr Phe Leu Gly Asp Tyr Phe Gly Ile Leu Lys Glu Ala

115 120 125

Arg Val Thr Val Phe Pro Phe Asn Ile Leu Asp Asn Pro Met Tyr Trp

130 135 140

Gly Ser Thr Ala Asn Tyr Leu Gly Trp Ala Ile Met His Ala Ser Pro

145 150 155 160

Thr Gly Leu Leu Leu Thr Val Leu Val Ala Leu Thr Tyr Ile Val Ala

165 170 175

Leu Leu Tyr Glu Glu Pro Phe Thr Ala Glu Ile Tyr Arg Gln Lys Ala

180 185 190

Ser Gly Ser His Lys-Arg Ser

195

<210> 7

<211> 229

<212> PRT

<213> Homo sapiens

<400> 7

Met Ala Pro His Gly Pro Gly Ser Leu Thr Thr Leu Val Pro Trp Ala

1 5 10 15

Ala Ala Leu Leu Leu Ala Leu Gly Val Glu Arg Ala Leu Ala Leu Pro

20 25 30

Glu Ile Cys Thr Gln Cys Pro Gly Ser Val Gln Asn Leu Ser Lys Val

35 40 45

Ala Phe Tyr Cys Lys Thr Thr Arg Glu Leu Met Leu His Ala Arg Cys

50 55 60

Cys Leu Asn Gln Lys Gly Thr Ile Leu Gly Leu Asp Leu Gln Asn Cys

65 70 75 80

Ser Leu Glu Asp Pro Gly Pro Asn Phe His Gln Ala His Thr Thr Val

85 90 95

Ile Ile Asp Leu Gln Ala Asn Pro Leu Lys Gly Asp Leu Ala Asn Thr

100 105 110

Phe Arg Gly Phe Thr Gln Leu Gln Thr Leu Ile Leu Pro Gln His Val

115 120 125

Asn Cys Pro Gly Gly Ile Asn Ala Trp Asn Thr Ile Thr Ser Tyr Ile

130 135 140

Asp Asn Gln Ile Cys Gln Gly Gln Lys Asn Leu Cys Asn Asn Thr Gly

145 150 155 160

Asp Pro Glu Met Cys Pro Glu Asn Gly Ser Cys Val Pro Asp Gly Pro

165 170 175

Gly Leu Leu Gln Cys Val Cys Ala Asp Gly Phe His Gly Tyr Lys Cys

180 185 190

Met Arg Gln Gly Ser Phe Ser Leu Leu Met Phe Phe Gly Ile Leu Gly

195 200 205

Ala Thr Thr Leu Ser Val Ser Ile Leu Leu Trp Ala Thr Gln Arg Arg

210 215 220

Lys Ala Lys Thr Ser

225

<210> 8

<211> 178

<212> PRT

<213> Homo sapiens

<400> 8

Met Ser Pro Ser Gly Arg Leu Cys Leu Leu Thr Ile Val Gly Leu Ile
1 5 10 15

Leu Pro Thr Arg Gly Gln Thr Leu Lys Asp Thr Thr Ser Ser Ser Ser
20 25 30

Ala Asp Ser Thr Ile Met Asp Ile Gln Val Pro Thr Arg Ala Pro Asp
35 40 45

Ala Val Tyr Thr Glu Leu Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro
50 55 60

Ala Asp Glu Thr Pro Gln Pro Gln Thr Gln Thr Gln Gln Leu Glu Gly
65 70 75 80

Thr Asp Gly Pro Leu Val Thr Asp Pro Glu Thr His Lys Ser Thr Lys
85 90 95

Ala Ala His Pro Thr Asp Asp Thr Thr Thr Leu Ser Glu Arg Pro Ser
100 105 110

Pro Ser Thr Asp Val Gln Thr Asp Pro Gln Thr Leu Lys Pro Ser Gly
115 120 125

Phe His Glu Asp Asp Pro Phe Phe Tyr Asp Glu His Thr Leu Arg Lys
130 135 140

Arg Gly Leu Leu Val Ala Ala Val Leu Phe Ile Thr Gly Ile Ile Ile
145 150 155 160

Leu Thr Ser Gly Lys Cys Arg Gln Leu Ser Arg Leu Cys Arg Asn His

165 170 175

Cys Arg

<210> 9

<211> 443

<212> PRT

<213> Homo sapiens

<400> 9

Met Arg Leu Thr Arg Lys Arg Leu Cys Ser Phe Leu Ile Ala Leu Tyr

1 5 10 15

Cys Leu Phe Ser Leu Tyr Ala Ala Tyr His Val Phe Phe Gly Arg Arg

20 25 30

Arg Gln Ala Pro Ala Gly Ser Pro Arg Gly Leu Arg Lys Gly Ala Ala

35 40 45

Pro Ala Arg Glu Arg Arg Gly Arg Glu Gln Ser Thr Leu Glu Ser Glu

50 55 60

Glu Trp Asn Pro Trp Glu Gly Asp Glu Lys Asn Glu Gln Gln His Arg

65 70 75 80

Phe Lys Thr Ser Leu Gln Ile Leu Asp Lys Ser Thr Lys Gly Lys Thr

85 90 95

Asp Leu Ser Val Gln Ile Trp Gly Lys Ala Ala Ile Gly Leu Tyr Leu

100 105 110

Trp Glu His Ile Phe Glu Gly Leu Leu Asp Pro Ser Asp Val Thr Ala

115 120 125

Gln Trp Arg Glu Gly Lys Ser Ile Val Gly Arg Thr Gln Tyr Ser Phe

130 135 140

Ile Thr Gly Pro Ala Val Ile Pro Gly Tyr Phe Ser Val Asp Val Asn

145 150 155 160

Asn Val Val Leu Ile Leu Asn Gly Arg Glu Lys Ala Lys Ile Phe Tyr

165 170 175

Ala Thr Gln Trp Leu Leu Tyr Ala Gln Asn Leu Val Gln Ile Gln Lys

180 185 190

Leu Gln His Leu Ala Val Val Leu Leu Gly Asn Glu His Cys Asp Asn

195 200 205

Glu Trp Ile Asn Pro Phe Leu Lys Arg Asn Gly Gly Phe Val Glu Leu

210 215 220

Leu Phe Ile Ile Tyr Asp Ser Pro Trp Ile Asn Asp Val Asp Val Phe

225 230 235 240

Gln Trp Pro Leu Gly Val Ala Thr Tyr Arg Asn Phe Pro Val Val Glu

245 250 255

Ala Ser Trp Ser Met Leu His Asp Glu Arg Pro Tyr Leu Cys Asn Phe

260 265 270

Leu Gly Thr Ile Tyr Glu Asn Ser Ser Arg Gln Ala Leu Met Asn Ile

275 280 285

Leu Lys Lys Asp Gly Asn Asp Lys Leu Cys Trp Val Ser Ala Arg Glu

290 295 300

His Trp Gln Pro Gln Glu Thr Asn Glu Ser Leu Lys Asn Tyr Gln Asp

305 310 315 320

Ala Leu Leu Gln Ser Asp Leu Thr Leu Cys Pro Val Gly Val Asn Thr

325 330 335

Glu Cys Tyr Arg Ile Tyr Glu Ala Cys Ser Tyr Gly Ser Ile Pro Val

340 345 350

Val Glu Asp Val Met Thr Ala Gly Asn Cys Gly Asn Thr Ser Val His

355 360 365

His Gly Ala Pro Leu Gln Leu Leu Lys Ser Met Gly Ala Pro Phe Ile

370 375 380

Phe Ile Lys Asn Trp Lys Glu Leu Pro Ala Val Leu Glu Lys Glu Lys

385 390 395 400

Thr Ile Ile Leu Gln Glu Lys Ile Glu Arg Arg Lys Met Leu Leu Gln

405 410 415

Trp Tyr Gln His Phe Lys Thr Glu Leu Lys Met Lys Phe Thr Asn Ile

420 425 430

Leu Glu Ser Ser Phe Leu Met Asn Asn Lys Ser

435 440

<210> 10

<211> 130

<212> PRT

<213> Homo sapiens

<400> 10

Met Glu Thr Leu Gly Ala Leu Leu Val Leu Glu Phe Leu Leu Leu Ser

1 5 10 15

Pro Val Glu Ala Gln Gln Ala Thr Glu His Arg Leu Lys Pro Trp Leu

20 25 30

Val Gly Leu Ala Ala Val Val Gly Phe Leu Phe Ile Val Tyr Leu Val

35 40 45

Leu Leu Ala Asn Arg Leu Trp Cys Ser Lys Ala Arg Ala Glu Asp Glu

50 55 60

Glu Glu Thr Thr Phe Arg Met Glu Ser Asn Leu Tyr Gln Asp Gln Ser

65 70 75 80

Glu Asp Lys Arg Glu Lys Lys Glu Ala Lys Glu Lys Glu Glu Lys Arg

85 90 95

Lys Lys Glu Lys Lys Thr Ala Lys Glu Gly Glu Ser Asn Leu Gly Leu

100 105 110

Asp Leu Glu Glu Lys Glu Pro Gly Asp His Glu Arg Ala Lys Ser Thr

115 120 125

Val Met

130

<210> 11

<211> 369

<212> DNA

<213> Homo sapiens

<400> 11

atgaaggctg tgctgcttgc cctgttgatg gcaggcttgg ccctgcagcc aggcactgcc 60

ctgctgtgct actcctgcaa agcccaggtg agcaacgagg actgcctgca ggtgaagaac 120

tgcacccagc tgggggagca gtgctggacc gcgcgcatcc gcgcagttgg cctcctgacc 180

gtcatcagca aaggctgcag cttgaactgc gtggatgact cacaggacta ctacgtgggc 240

aagaagaaca tcacgtgctg tgacaccgac ttgtgcaacg ccagcggggc ccatgccctg 300

cagccggctg ccgccatcct tgcgctgctc cctgcactcg gcctgctgct ctggggaccc 360

ggccagcta 369

<210> 12

<211> 660

<212> DNA

<213> Homo sapiens

<400> 12

atgtccatgg gcctggagat cacgggcacc gcgctggccg tgctgggctg gctgggcacc 60

atcgtgtgct gcgcgttgcc catgtggcgc gtgtcggcct tcatcggcag caacatcatc 120

acgtcgcaga acatctggga gggcctgtgg atgaactgcg tggtgcagag caccggccag 180

atgcagtgca aggtgtacga ctcgctgctg gcactgccac aggaccttca ggcggcccgc 240

gccctcatcg tggtggccat cctgctggcc gccttcgggc tgctagtggc gctggtgggc 300

gcccagtgca ccaactgcgt gcaggacgac acggccaagg ccaagatcac catcgtggca 360

ggcgtgctgt tccttctcgc cgccctgctc accctcgtgc cggtgtcctg gtcggccaac 420

accattatcc gggacttcta caacccgtg gtgcccgagg cgcagaagcg cgagatgggc 480

gcgggcctgt acgtgggctg ggcggccgcg gcgctgcagc tgctgggggg cgcgctgctc 540

tgctgctcgt gtcccccacg cgagaagaag tacacggcca ccaaggtcgt ctactccgcg 600

ccgcgctcca ccggcccggg agccagcctg ggcacaggct acgaccgcaa ggactacgtc 660

<210> 13

<211> 243

<212> DNA

<213> Homo sapiens

<400> 13

atggcgtatc acggcctcac tgtgcctctc attgtgatga gcgtgttctg gggcttcgtc 60

ggcttcttgg tgccttggtt catccctaag ggtcctaacc ggggagttat cattaccatg 120

ttggtgacct gttcagtttg ctgctatctc ttttggctga ttgcaattct ggcccaactc 180

aaccctctct ttggaccgca attgaaaaat gaaaccatct ggtatctgaa gtatcattgg 240

cct 243

<210> 14

<211> 903

<212> DNA

<213> Homo sapiens

<400> 14

atgctagcct tgcgcgtggc gcgcggctcg tgggggggccc tgcgcggcgc cgcttgggct 60

ccgggaacgc ggccgagtaa gcgacgcgcc tgctgggccc tgctgccgcc cgtgccctgc 120

tgcttgggct gcctggccga acgctggagg ctgcgtccgg ccgctcttgg cttgcggctg 180

cccgggatcg gccagcggaa ccactgttcg ggcgcgggga aggcggctcc caggccagcg 240

gccggagcgg gcgccgctgc cgaagccccg ggcggccagt ggggcccggc gagcaccccc 300

agcctgtatg aaaacccatg gacaatcccg aatatgttgt caatgacgag aattggcttg 360

gccccagttc tgggctattt gattattgaa gaagatttta atattgcact aggagttttt 420

gctttagctg gactaacaga tttgttggat ggatttattg ctcgaaactg ggccaatcaa 480

agatcagctt tgggaagtgc tcttgatcca cttgctgata aaatacttat cagtatctta 540

tatgttagct tgacctatgc agatcttatt ccagttccac ttacttacat gatcatttcg 600

agagatgtaa tgttgattgc tgctgttttt tatgtcagat accgaactct tccaacacca 660

cgaacacttg ccaagtattt caatccttgc tatgccactg ctaggttaaa accaacattc 720

atcagcaagg tgaatacagc agtccagtta atcttggtgg cagcttcttt ggcagctcca 780

gttttcaact atgctgacag catttatctt cagatactat ggtgttttac agctttcacc 840

acagctgcat cagcttatag ttactatcat tatggccgga agactgttca ggtgataaaa 900

gac 903

<210> 15

<211> 1149

<212> DNA

<213> Homo sapiens

<400> 15

atggaggcgc tggggaagct gaagcagttc gatgcctacc ccaagacttt ggaggacttc 60

cgggtcaaga cctgcggggg cgccaccgtg accattgtca gtggcctttct catgctgcta 120

ctgttcctgt ccgagctgca gtattacctc accacggagg tgcatcctga gctctacgtg 180

gacaagtcgc ggggagataa actgaagatc aacatcgatg tactttttcc gcacatgcct 240

tgtgcctatc tgagtattga tgccatggat gtggccggag aacagcagct ggatgtggaa 300

cacaacctgt tcaagcaacg actagataaa gatggcatcc ccgtgagctc agaggctgag 360

cggcatgagc ttgggaaagt cgaggtgacg gtgtttgacc ctgactccct ggaccctgat 420

cgctgtgaga gctgctatgg tgctgaggca gaagatatca agtgctgtaa cacctgtgaa 480

gatgtgcggg aggcatatcg ccgtagaggc tgggccttca agaacccaga tactattgag 540

cagtgccggc gagagggctt cagccagaag atgcaggagc agaagaatga aggctgccag 600

gtgtatggct tcttggaagt caataaggtg gccggaaact tccactttgc ccctgggaag 660

agcttccagc agtcccatgt gcacgtccat gacttgcaga gctttggcct tgacaacatc 720

aacatgaccc actacatcca gcacctgtca tttggggagg actatccagg cattgtgaac 780

cccctggacc acaccaatgt cactgcgccc caagcctcca tgatgttcca gtactttgtg 840

aaggtggtgc ccactgtgta catgaaggtg gacggagagg tactgaggac aaatcagttc 900

tctgtgacca gacatgagaa ggttgccaat gggctgttgg gcgaccaagg ccttcccgga 960

gtcttcgtcc tctatgagct ctcgcccatg atggtgaagc tgacggagaa gcacaggtcc 1020

ttcacccact tcctgacagg tgtgtgcgcc atcattgggg gcatgttcac agtggctgga 1080

ctcatcgatt cgctcatcta ccactcagca cgagccatcc agaagaaaat tgatctaggg 1140

aagacaacg 1149

<210> 16

<211> 597

<212> DNA

<213> Homo sapiens

<400> 16

atgacccggc tgctgggcta cgtggacccc ctggatccca gctttgtggc tgccgtcatc 60

accatcacct tcaatccgct ctactggaat gtggttgcac gatgggaaca caagacccgc 120

aagctgagca gggccttcgg atccccctac ctggcctgct actctctaag cgtcaccatc 180

ctgctcctga acttcctgcg ctcgcactgc ttcacgcagg ccatgctgag ccagcccagg 240

atggagagcc tggacacccc cgcggcctac agcctgggcc tcgcgctcct gggactgggc 300

gtcgtgctcg tgctctccag cttctttgca ctggggttcg ctggaacttt cctaggtgat 360

tacttcggga tcctcaagga ggcgagagtg accgtgttcc ccttcaacat cctggacaac 420

cccatgtact ggggaagcac agccaactac ctgggctggg ccatcatgca cgccagcccc 480

acgggcctgc tcctgacggt gctggtggcc ctcacctaca tagtggctct cctatacgaa 540

gagcccttca ccgctgagat ctaccggcag aaagcctccg ggtcccacaa gaggagc 597

<210> 17

<211> 687

<212> DNA

<213> Homo sapiens

<400> 17

atggcgcctc acggcccggg tagtcttacg accctggtgc cctgggctgc cgccctgctc 60
ctcgctctgg gcgtggaaag ggctctggcg ctacccgaga tatgcaccca atgtccaggg 120
agcgtgcaaa atttgtcaaa agtggccttt tattgtaaaa cgacacgaga gctaatgctg 180
catgccccgtt gctgcctgaa tcagaagggc accatcttgg ggctggatct ccagaactgt 240
tctctggagg accctggtcc aaactttcat caggcacata ccactgtcat catagacctg 300
caagcaaacc ccctcaaagg tgacttggcc aacaccttcc gtggctttac tcagctccag 360
actctgatac tgccacaaca tgtcaactgt cctggaggaa ttaatgcctg gaatactatc 420
acctcttata tagacaacca aatctgtcaa gggcaaaaga acctttgcaa taacactggg 480
gacccagaaa tgtgtcctga gaatggatct tgtgtacctg atggtccagg tcttttgcag 540
tgtgtttgtg ctgatggttt ccatggatac aagtgtatgc gccagggctc gttctcactg 600
cttatgttct tcgggattct gggagccacc actctatccg tctccattct gctttgggcg 660
acccagcgcc gaaaagccaa gacttca 687

<210> 18

<211> 534

<212> DNA

<213> Homo sapiens

<400> 18

atgtcgccct ctggtcgcct gtgtcttctc accatcgttg gcctgattct ccccaccaga 60
ggacagacgt tgaaagatac cacgtccagt tcttcagcag actcaactat catggacatt 120
caggtcccga cacgagcccc agatgcagtc tacacagaac tccagcccac ctctccaacc 180
ccaacctggc ctgctgatga aacaccacaa ccccagaccc agacccagca actggaagga 240
acggatgggc ctctagtgac agatccagag acacacaaga gcaccaaagc agctcatccc 300
actgatgaca ccacgacgct ctctgagaga ccatccccaa gcacagacgt ccagacagac 360

ccccagaccc tcaagccatc tggttttcat gaggatgacc ccttcttcta tgatgaacac 420
accctccgga aacgggggct gttggtcgca gctgtgctgt tcatcacagg catcatcatc 480
ctcaccagtg gcaagtgcag gcagctgtcc cggttatgcc ggaatcattg cagg 534

<210> 19
<211> 1329
<212> DNA
<213> Homo sapiens

<400> 19
atgcggctga cgcggaagcg gctctgctcg tttcttatcg ccctgtactg cctattctcc 60
ctctacgctg cctaccacgt cttcttcggg cgccgccgcc aggcgccggc cgggtccccg 120
cggggcctca ggaagggggc ggcccccgcg cgggagagac gcggccgaga acagtccact 180
ttggaaagtg aagaatggaa tccttgggaa ggagatgaaa aaaatgagca acaacacaga 240
tttaaaacta gccttcaaat attagataaa tccacgaaag gaaaaacaga tctcagtgta 300
caaatctggg gcaaagctgc cattggcttg tatctctggg agcatatttt tgaaggctta 360
cttgatccca gcgatgtgac tgctcaatgg agagaaggaa agtcaatcgt aggaagaaca 420
cagtacagct tcatcactgg tccagctgta ataccagggt acttctccgt tgatgtgaat 480
aatgtggtac tcattttaaa tggaagagaa aaagcaaaga tcttttatgc cacccagtgg 540
ttactttatg cacaaaattt agtgcaaatt caaaaactcc agcatcttgc tgttgttttg 600
ctcggaaatg aacattgtga taatgagtgg ataaacccat tcctcaaaag aaatggaggc 660
ttcgtggagc tgcttttcat aatatatgac agcccctgga ttaatgacgt ggatgttttt 720
cagtggcctt taggagtagc aacatacagg aattttcctg tggtggaggc aagttggtca 780
atgctgcatg atgagaggcc atatttatgt aatttcttag gaacgattta tgaaaattca 840
tccagacagg cactaatgaa cattttgaaa aaagatggga acgataagct ttgttgggtt 900
tcagcaagag aacactggca gcctcaggaa acaaatgaaa gtcttaagaa ttaccaagat 960

gccttgcttc agagtgatct cacattgtgc ccggtcggag taaacacaga atgctatcga 1020
atctatgagg cttgctccta tggctccatt cctgtggtgg aagacgtgat gacagctggc 1080
aactgtggga atacatctgt gcaccacggt gctcctctgc agttactcaa gtccatgggt 1140
gctcccttta tctttatcaa gaactggaag gaactccctg ctgttttaga aaaagagaaa 1200
actataattt tacaagaaaa aattgaaaga agaaaaatgt tacttcagtg gtatcagcac 1260
ttcaagacag agcttaaaat gaaatttact aatattttag aaagctcatt tttaatgaat 1320
aataaaagt 1329

<210> 20
<211> 390
<212> DNA
<213> Homo sapiens

<400> 20
atggagaccc tgggggccct tctggtgctg gagtttctgc tcctctcccc ggtggaggcc 60
cagcaggcca cggagcatcg cctgaagccg tggctggtgg gcctggctgc ggtagtcggc 120
ttcctgttca tcgtctattt ggtcttgctg gccaaccgcc tctggtgttc caaggccagg 180
gctgaggacg aggaggagac cacgttcaga atggagtcca acctatacca ggaccagagt 240
gaagacaaga gagagaagaa agaggccaag gagaaagaag agaagaggaa gaaggagaaa 300
aagacagcaa aggaaggaga gagcaacttg ggactggatc tggaggaaaa agagcccgga 360
gaccatgaga gagcaaagag cacagtcatg 390

<210> 21
<211> 979
<212> DNA

<213> Homo sapiens

<400> 21

```
agcccaccag tgacc atg aag gct gtg ctg ctt gcc ctg ttg atg gca ggc        51
                 Met Lys Ala Val Leu Leu Ala Leu Leu Met Ala Gly
                 1               5                   10
ttg gcc ctg cag cca ggc act gcc ctg ctg tgc tac tcc tgc aaa gcc          99
Leu Ala Leu Gln Pro Gly Thr Ala Leu Leu Cys Tyr Ser Cys Lys Ala
        15                  20                  25
cag gtg agc aac gag gac tgc ctg cag gtg aag aac tgc acc cag ctg         147
Gln Val Ser Asn Glu Asp Cys Leu Gln Val Lys Asn Cys Thr Gln Leu
    30                  35                  40
ggg gag cag tgc tgg acc gcg cgc atc cgc gca gtt ggc ctc ctg acc         195
Gly Glu Gln Cys Trp Thr Ala Arg Ile Arg Ala Val Gly Leu Leu Thr
45                  50                  55                  60
gtc atc agc aaa ggc tgc agc ttg aac tgc gtg gat gac tca cag gac         243
Val Ile Ser Lys Gly Cys Ser Leu Asn Cys Val Asp Asp Ser Gln Asp
                65                  70                  75
tac tac gtg ggc aag aag aac atc acg tgc tgt gac acc gac ttg tgc         291
Tyr Tyr Val Gly Lys Lys Asn Ile Thr Cys Cys Asp Thr Asp Leu Cys
            80                  85                  90
aac gcc agc ggg gcc cat gcc ctg cag ccg gct gcc gcc atc ctt gcg         339
Asn Ala Ser Gly Ala His Ala Leu Gln Pro Ala Ala Ala Ile Leu Ala
        95                  100                 105
ctg ctc cct gca ctc ggc ctg ctg ctc tgg gga ccc ggc cag cta             384
Leu Leu Pro Ala Leu Gly Leu Leu Leu Trp Gly Pro Gly Gln Leu
    110                 115                 120
```

taggct ctggggggcc ccgctgcagc ccacactggg tgtggtgccc caggcctctg 440

tgccactcct cacagacctg gcccagtggg agcctgtcct ggttcctgag gcacatccta 500

acgcaagtct gaccatgtat gtctgcaccc ctgtccccca ccctgaccct cccatggccc 560

tctccaggac tcccacccgg cagatcagct ctagtgacac agatccgcct gcagatggcc 620

cctccaaccc tctctgctgc tgtttccatg gcccagcatt ctccaccctt aaccctgtgc 680

tcaggcacct cttcccccag gaagccttcc ctgcccaccc catctatgac ttgagccagg 740

tctggtccgt ggtgtccccc gcacccagca ggggacaggc actcaggagg gcccagtaaa 800

ggctgagatg aagtggactg agtagaactg gaggacaaga gtcgacgtga gttcctggga 860

gtctccagag atggggcctg gaggcctgga ggaaggggcc aggcctcaca ttcgtggggc 920

tccctgaatg gcagcctgag cacagcgtag gcccttaata aacacctgtt ggataagcc 979

<210> 22

<211> 123

<212> PRT

<213> Homo sapiens

<400> 22

Met Lys Ala Val Leu Leu Ala Leu Leu Met Ala Gly

1 5 10

Leu Ala Leu Gln Pro Gly Thr Ala Leu Leu Cys Tyr Ser Cys Lys Ala

15 20 25

Gln Val Ser Asn Glu Asp Cys Leu Gln Val Lys Asn Cys Thr Gln Leu

30 35 40

Gly Glu Gln Cys Trp Thr Ala Arg Ile Arg Ala Val Gly Leu Leu Thr

45 50 55 60

Val Ile Ser Lys Gly Cys Ser Leu Asn Cys Val Asp Asp Ser Gln Asp

65 70 75

Tyr Tyr Val Gly Lys Lys Asn Ile Thr Cys Cys Asp Thr Asp Leu Cys

80 85 90

Asn Ala Ser Gly Ala His Ala Leu Gln Pro Ala Ala Ala Ile Leu Ala

95 100 105

Leu Leu Pro Ala Leu Gly Leu Leu Leu Trp Gly Pro Gly Gln Leu

110 115 120

<210> 23

<211> 1279

<212> DNA

<213> Homo sapiens

<400> 23

agggccagcc cagtcgccgc cgcccgccca caaagccaca ggcaggtgca ggcgcagccg 60

cggcgagagc gtatggagcc gagccgttag cgcgcgccgt cggtgagtca gtccgtccgt 120

ccgtccgtcc gtcggggcgc cgcagctccc gccaggccca gcggccccgg cccctcgtct 180

ccccgcaccc ggagccaccc ggtggagcgg gccttgccgc ggcagcc atg tcc atg 236

Met Ser Met

1

ggc ctg gag atc acg ggc acc gcg ctg gcc gtg ctg ggc tgg ctg ggc 284

Gly Leu Glu Ile Thr Gly Thr Ala Leu Ala Val Leu Gly Trp Leu Gly

5 10 15

acc atc gtg tgc tgc gcg ttg ccc atg tgg cgc gtg tcg gcc ttc atc 332

Thr Ile Val Cys Cys Ala Leu Pro Met Trp Arg Val Ser Ala Phe Ile

20 25 30 35

```
ggc agc aac atc atc acg tcg cag aac atc tgg gag ggc ctg tgg atg     380
Gly Ser Asn Ile Ile Thr Ser Gln Asn Ile Trp Glu Gly Leu Trp Met
                 40                  45                  50
aac tgc gtg gtg cag agc acc ggc cag atg cag tgc aag gtg tac gac     428
Asn Cys Val Val Gln Ser Thr Gly Gln Met Gln Cys Lys Val Tyr Asp
             55                  60                  65
tcg ctg ctg gca ctg cca cag gac ctt cag gcg gcc cgc gcc ctc atc     476
Ser Leu Leu Ala Leu Pro Gln Asp Leu Gln Ala Ala Arg Ala Leu Ile
         70                  75                  80
gtg gtg gcc atc ctg ctg gcc gcc ttc ggg ctg cta gtg gcg ctg gtg     524
Val Val Ala Ile Leu Leu Ala Ala Phe Gly Leu Leu Val Ala Leu Val
     85                  90                  95
ggc gcc cag tgc acc aac tgc gtg cag gac gac acg gcc aag gcc aag     572
Gly Ala Gln Cys Thr Asn Cys Val Gln Asp Asp Thr Ala Lys Ala Lys
100                 105                 110                 115
atc acc atc gtg gca ggc gtg ctg ttc ctt ctc gcc gcc ctg ctc acc     620
Ile Thr Ile Val Ala Gly Val Leu Phe Leu Leu Ala Ala Leu Leu Thr
                120                 125                 130
ctc gtg ccg gtg tcc tgg tcg gcc aac acc att atc cgg gac ttc tac     668
Leu Val Pro Val Ser Trp Ser Ala Asn Thr Ile Ile Arg Asp Phe Tyr
            135                 140                 145
aac ccc gtg gtg ccc gag gcg cag aag cgc gag atg ggc gcg ggc ctg     716
Asn Pro Val Val Pro Glu Ala Gln Lys Arg Glu Met Gly Ala Gly Leu
        150                 155                 160
tac gtg ggc tgg gcg gcc gcg gcg ctg cag ctg ctg ggg ggc gcg ctg     764
Tyr Val Gly Trp Ala Ala Ala Ala Leu Gln Leu Leu Gly Gly Ala Leu
    165                 170                 175
```

ctc tgc tgc tcg tgt ccc cca cgc gag aag aag tac acg gcc acc aag 812
Leu Cys Cys Ser Cys Pro Pro Arg Glu Lys Lys Tyr Thr Ala Thr Lys
180 185 190 195
gtc gtc tac tcc gcg ccg cgc tcc acc ggc ccg gga gcc agc ctg ggc 860
Val Val Tyr Ser Ala Pro Arg Ser Thr Gly Pro Gly Ala Ser Leu Gly
200 205 210
aca ggc tac gac cgc aag gac tac gtc taa gggacagacg cagggagacc 910
Thr Gly Tyr Asp Arg Lys Asp Tyr Val
215 220
ccaccaccac caccaccacc aacaccacca ccaccacagc gagctggagc gcgcaccagg 970
ccatccagcg tgcagccttg cctcggaggc cagcccaccc ccagaagcca ggaagccccc 1030
gcgctggact ggggcagctt ccccagcagc cacggctttg cgggccgggc agtcgacttc 1090
ggggcccagg gaccaacctg catggactgt gaaacctcac ccttctggag cacggggcct 1150
gggtgaccgc caatacttga ccaccccgtc gagccccatc gggccgctgc cccatgctc 1210
gcgctgggca gggaccggca gccctggaag gggcacttga tatttttcaa taaaagcctt 1270
tcgttttgc 1279

<210> 24
<211> 220
<212> PRT
<213> Homo sapiens

<400> 24
Met Ser Met
1
Gly Leu Glu Ile Thr Gly Thr Ala Leu Ala Val Leu Gly Trp Leu Gly

5 10 15

Thr Ile Val Cys Cys Ala Leu Pro Met Trp Arg Val Ser Ala Phe Ile

20 25 30 35

Gly Ser Asn Ile Ile Thr Ser Gln Asn Ile Trp Glu Gly Leu Trp Met

40 45 50

Asn Cys Val Val Gln Ser Thr Gly Gln Met Gln Cys Lys Val Tyr Asp

55 60 65

Ser Leu Leu Ala Leu Pro Gln Asp Leu Gln Ala Ala Arg Ala Leu Ile

70 75 80

Val Val Ala Ile Leu Leu Ala Ala Phe Gly Leu Leu Val Ala Leu Val

85 90 95

Gly Ala Gln Cys Thr Asn Cys Val Gln Asp Asp Thr Ala Lys Ala Lys

100 105 110 115

Ile Thr Ile Val Ala Gly Val Leu Phe Leu Leu Ala Ala Leu Leu Thr

120 125 130

Leu Val Pro Val Ser Trp Ser Ala Asn Thr Ile Ile Arg Asp Phe Tyr

135 140 145

Asn Pro Val Val Pro Glu Ala Gln Lys Arg Glu Met Gly Ala Gly Leu

150 155 160

Tyr Val Gly Trp Ala Ala Ala Ala Leu Gln Leu Leu Gly Gly Ala Leu

165 170 175

Leu Cys Cys Ser Cys Pro Pro Arg Glu Lys Lys Tyr Thr Ala Thr Lys

180 185 190 195

Val Val Tyr Ser Ala Pro Arg Ser Thr Gly Pro Gly Ala Ser Leu Gly

200 205 210

Thr Gly Tyr Asp Arg Lys Asp Tyr Val

215 220

<210> 25

<211> 835

<212> DNA

<213> Homo sapiens

<400> 25

gacacttcct ggtgggatcc gagtgaggcg acggggtagg ggttggcgct caggcggcga 60

cc atg gcg tat cac ggc ctc act gtg cct ctc att gtg atg agc gtg 107

Met Ala Tyr His Gly Leu Thr Val Pro Leu Ile Val Met Ser Val

1 5 10 15

ttc tgg ggc ttc gtc ggc ttc ttg gtg cct tgg ttc atc cct aag ggt 155

Phe Trp Gly Phe Val Gly Phe Leu Val Pro Trp Phe Ile Pro Lys Gly

20 25 30

cct aac cgg gga gtt atc att acc atg ttg gtg acc tgt tca gtt tgc 203

Pro Asn Arg Gly Val Ile Ile Thr Met Leu Val Thr Cys Ser Val Cys

35 40 45

tgc tat ctc ttt tgg ctg att gca att ctg gcc caa ctc aac cct ctc 251

Cys Tyr Leu Phe Trp Leu Ile Ala Ile Leu Ala Gln Leu Asn Pro Leu

50 55 60

ttt gga ccg caa ttg aaa aat gaa acc atc tgg tat ctg aag tat cat 299

Phe Gly Pro Gln Leu Lys Asn Glu Thr Ile Trp Tyr Leu Lys Tyr His

65 70 75

tgg cct tgagg aagaagacat gctctacagt gctcagtctt tgaggtcacg 350

Trp Pro

80

agaagagaat gccttctaga tgcaaaatca cctccaaacc agaccacttt tcttgacttg 410

cctgttttgg ccattagctg ccttaaacgt taacagcaca tttgaatgcc ttattctaca 470

atgcagcgtg ttttcctttg cctttttgc actttggtga attacgtgcc tccataacct 530

gaactgtgcc gactccacaa aacgattatg tactcttctg agatagaaga tgctgttctt 590

ctgagagata cgttactctc tccttggaat ctgtggattt gaagatggct cctgccttct 650

cacgtgggaa tcagtgaagt gtttagaaac tgctgcaaga caaacaagac tccagtgggg 710

tggtcagtag gagagcacgt tcagagggaa gagccatctc aacagaatcg caccaaacta 770

tactttcagg atgaatttct tctttctgcc atcttttgga ataaatattt tcctcctttc 830

tatgg 835

<210> 26

<211> 81

<212> PRT

<213> Homo sapiens

<400> 26

Met Ala Tyr His Gly Leu Thr Val Pro Leu Ile Val Met Ser Val
1 5 10 15

Phe Trp Gly Phe Val Gly Phe Leu Val Pro Trp Phe Ile Pro Lys Gly
20 25 30

Pro Asn Arg Gly Val Ile Ile Thr Met Leu Val Thr Cys Ser Val Cys
35 40 45

Cys Tyr Leu Phe Trp Leu Ile Ala Ile Leu Ala Gln Leu Asn Pro Leu
50 55 60

Phe Gly Pro Gln Leu Lys Asn Glu Thr Ile Trp Tyr Leu Lys Tyr His
65 70 75

Trp Pro

80

<210> 27

<211> 1256

<212> DNA

<213> Homo sapiens

<400> 27

agtatggagg caccggtagc ccagtgtctg agtggttgcc gggtctccat ggagaagcgg 60

ctcgccagtg tcccaggctg ctgagctctc gccgcccgag accccgcggc gcggccgcag 120

ggcc atg cta gcc ttg cgc gtg gcg cgc ggc tcg tgg ggg gcc ctg cgc 169

Met Leu Ala Leu Arg Val Ala Arg Gly Ser Trp Gly Ala Leu Arg

1 5 10 15

ggc gcc gct tgg gct ccg gga acg cgg ccg agt aag cga cgc gcc tgc 217

Gly Ala Ala Trp Ala Pro Gly Thr Arg Pro Ser Lys Arg Arg Ala Cys

20 25 30

tgg gcc ctg ctg ccg ccc gtg ccc tgc tgc ttg ggc tgc ctg gcc gaa 265

Trp Ala Leu Leu Pro Pro Val Pro Cys Cys Leu Gly Cys Leu Ala Glu

35 40 45

cgc tgg agg ctg cgt ccg gcc gct ctt ggc ttg cgg ctg ccc ggg atc 313

Arg Trp Arg Leu Arg Pro Ala Ala Leu Gly Leu Arg Leu Pro Gly Ile

50 55 60

ggc cag cgg aac cac tgt tcg ggc gcg ggg aag gcg gct ccc agg cca 361

Gly Gln Arg Asn His Cys Ser Gly Ala Gly Lys Ala Ala Pro Arg Pro

65 70 75

gcg gcc gga gcg ggc gcc gct gcc gaa gcc ccg ggc ggc cag tgg ggc 409
Ala Ala Gly Ala Gly Ala Ala Ala Glu Ala Pro Gly Gly Gln Trp Gly
80 85 90 95

ccg gcg agc acc ccc agc ctg tat gaa aac cca tgg aca atc ccg aat 457
Pro Ala Ser Thr Pro Ser Leu Tyr Glu Asn Pro Trp Thr Ile Pro Asn
100 105 110

atg ttg tca atg acg aga att ggc ttg gcc cca gtt ctg ggc tat ttg 505
Met Leu Ser Met Thr Arg Ile Gly Leu Ala Pro Val Leu Gly Tyr Leu
115 120 125

att att gaa gaa gat ttt aat att gca cta gga gtt ttt gct tta gct 553
Ile Ile Glu Glu Asp Phe Asn Ile Ala Leu Gly Val Phe Ala Leu Ala
130 135 140

gga cta aca gat ttg ttg gat gga ttt att gct cga aac tgg gcc aat 601
Gly Leu Thr Asp Leu Leu Asp Gly Phe Ile Ala Arg Asn Trp Ala Asn
145 150 155

caa aga tca gct ttg gga agt gct ctt gat cca ctt gct gat aaa ata 649
Gln Arg Ser Ala Leu Gly Ser Ala Leu Asp Pro Leu Ala Asp Lys Ile
160 165 170 175

ctt atc agt atc tta tat gtt agc ttg acc tat gca gat ctt att cca 697
Leu Ile Ser Ile Leu Tyr Val Ser Leu Thr Tyr Ala Asp Leu Ile Pro
180 185 190

gtt cca ctt act tac atg atc att tcg aga gat gta atg ttg att gct 745
Val Pro Leu Thr Tyr Met Ile Ile Ser Arg Asp Val Met Leu Ile Ala
195 200 205

gct gtt ttt tat gtc aga tac cga act ctt cca aca cca cga aca ctt 793
Ala Val Phe Tyr Val Arg Tyr Arg Thr Leu Pro Thr Pro Arg Thr Leu
210 215 220

gcc aag tat ttc aat cct tgc tat gcc act gct agg tta aaa cca aca 841
Ala Lys Tyr Phe Asn Pro Cys Tyr Ala Thr Ala Arg Leu Lys Pro Thr
225 230 235

ttc atc agc aag gtg aat aca gca gtc cag tta atc ttg gtg gca gct 889
Phe Ile Ser Lys Val Asn Thr Ala Val Gln Leu Ile Leu Val Ala Ala
240 245 250 255

tct ttg gca gct cca gtt ttc aac tat gct gac agc att tat ctt cag 937
Ser Leu Ala Ala Pro Val Phe Asn Tyr Ala Asp Ser Ile Tyr Leu Gln
260 265 270

ata cta tgg tgt ttt aca gct ttc acc aca gct gca tca gct tat agt 985
Ile Leu Trp Cys Phe Thr Ala Phe Thr Thr Ala Ala Ser Ala Tyr Ser
275 280 285

tac tat cat tat ggc cgg aag act gtt cag gtg ata aaa gac tga 1030
Tyr Tyr His Tyr Gly Arg Lys Thr Val Gln Val Ile Lys Asp
290 295 300

tgaaagtcat ccctcactgt tagtaaggaa gcagtataca tcaatgggaa cagggcccat 1090
ggaaatgtac aggagtttcc ctattttggt gttcagcttg aaaaaggact tgtcagaatc 1150
aactgtgtca tcaaaattta agtaatgtgc attgaaaata aggttgatca tgggaatatg 1210
cagaatttcc aatgtatttt taaatacaaa taaaattgta atttag 1256

<210> 28
<211> 301
<212> PRT
<213> Homo sapiens

<400> 28

Met Leu Ala Leu Arg Val Ala Arg Gly Ser Trp Gly Ala Leu Arg
1 5 10 15
Gly Ala Ala Trp Ala Pro Gly Thr Arg Pro Ser Lys Arg Arg Ala Cys
20 25 30
Trp Ala Leu Leu Pro Pro Val Pro Cys Cys Leu Gly Cys Leu Ala Glu
35 40 45
Arg Trp Arg Leu Arg Pro Ala Ala Leu Gly Leu Arg Leu Pro Gly Ile
50 55 60
Gly Gln Arg Asn His Cys Ser Gly Ala Gly Lys Ala Ala Pro Arg Pro
65 70 75
Ala Ala Gly Ala Gly Ala Ala Ala Glu Ala Pro Gly Gly Gln Trp Gly
80 85 90 95
Pro Ala Ser Thr Pro Ser Leu Tyr Glu Asn Pro Trp Thr Ile Pro Asn
100 105 110
Met Leu Ser Met Thr Arg Ile Gly Leu Ala Pro Val Leu Gly Tyr Leu
115 120 125
Ile Ile Glu Glu Asp Phe Asn Ile Ala Leu Gly Val Phe Ala Leu Ala
130 135 140
Gly Leu Thr Asp Leu Leu Asp Gly Phe Ile Ala Arg Asn Trp Ala Asn
145 150 155
Gln Arg Ser Ala Leu Gly Ser Ala Leu Asp Pro Leu Ala Asp Lys Ile
160 165 170 175
Leu Ile Ser Ile Leu Tyr Val Ser Leu Thr Tyr Ala Asp Leu Ile Pro
180 185 190
Val Pro Leu Thr Tyr Met Ile Ile Ser Arg Asp Val Met Leu Ile Ala
195 200 205
Ala Val Phe Tyr Val Arg Tyr Arg Thr Leu Pro Thr Pro Arg Thr Leu

210 215 220

Ala Lys Tyr Phe Asn Pro Cys Tyr Ala Thr Ala Arg Leu Lys Pro Thr

225 230 235

Phe Ile Ser Lys Val Asn Thr Ala Val Gln Leu Ile Leu Val Ala Ala

240 245 250 255

Ser Leu Ala Ala Pro Val Phe Asn Tyr Ala Asp Ser Ile Tyr Leu Gln

260 265 270

Ile Leu Trp Cys Phe Thr Ala Phe Thr Thr Ala Ala Ser Ala Tyr Ser

275 280 285

Tyr Tyr His Tyr Gly Arg Lys Thr Val Gln Val Ile Lys Asp

290 295 300

<210> 29

<211> 1305

<212> DNA

<213> Homo sapiens

<400> 29

cttttttcc ggccggtccc c atg gag gcg ctg ggg aag ctg aag cag ttc 51

Met Glu Ala Leu Gly Lys Leu Lys Gln Phe

1 5 10

gat gcc tac ccc aag act ttg gag gac ttc cgg gtc aag acc tgc ggg 99

Asp Ala Tyr Pro Lys Thr Leu Glu Asp Phe Arg Val Lys Thr Cys Gly

15 20 25

ggc gcc acc gtg acc att gtc agt ggc ctt ctc atg ctg cta ctg ttc 147

Gly Ala Thr Val Thr Ile Val Ser Gly Leu Leu Met Leu Leu Leu Phe

30 35 40

ctg tcc gag ctg cag tat tac ctc acc acg gag gtg cat cct gag ctc 195

Leu Ser Glu Leu Gln Tyr Tyr Leu Thr Thr Glu Val His Pro Glu Leu

45 50 55

tac gtg gac aag tcg cgg gga gat aaa ctg aag atc aac atc gat gta 243

Tyr Val Asp Lys Ser Arg Gly Asp Lys Leu Lys Ile Asn Ile Asp Val

60 65 70

ctt ttt ccg cac atg cct tgt gcc tat ctg agt att gat gcc atg gat 291

Leu Phe Pro His Met Pro Cys Ala Tyr Leu Ser Ile Asp Ala Met Asp

75 80 85 90

gtg gcc gga gaa cag cag ctg gat gtg gaa cac aac ctg ttc aag caa 339

Val Ala Gly Glu Gln Gln Leu Asp Val Glu His Asn Leu Phe Lys Gln

95 100 105

cga cta gat aaa gat ggc atc ccc gtg agc tca gag gct gag cgg cat 387

Arg Leu Asp Lys Asp Gly Ile Pro Val Ser Ser Glu Ala Glu Arg His

110 115 120

gag ctt ggg aaa gtc gag gtg acg gtg ttt gac cct gac tcc ctg gac 435

Glu Leu Gly Lys Val Glu Val Thr Val Phe Asp Pro Asp Ser Leu Asp

125 130 135

cct gat cgc tgt gag agc tgc tat ggt gct gag gca gaa gat atc aag 483

Pro Asp Arg Cys Glu Ser Cys Tyr Gly Ala Glu Ala Glu Asp Ile Lys

140 145 150

tgc tgt aac acc tgt gaa gat gtg cgg gag gca tat cgc cgt aga ggc 531

Cys Cys Asn Thr Cys Glu Asp Val Arg Glu Ala Tyr Arg Arg Arg Gly

155 160 165 170

tgg gcc ttc aag aac cca gat act att gag cag tgc cgg cga gag ggc 579

Trp Ala Phe Lys Asn Pro Asp Thr Ile Glu Gln Cys Arg Arg Glu Gly

175 180 185

ttc agc cag aag atg cag gag cag aag aat gaa ggc tgc cag gtg tat 627

Phe Ser Gln Lys Met Gln Glu Gln Lys Asn Glu Gly Cys Gln Val Tyr

190 195 200

ggc ttc ttg gaa gtc aat aag gtg gcc gga aac ttc cac ttt gcc cct 675

Gly Phe Leu Glu Val Asn Lys Val Ala Gly Asn Phe His Phe Ala Pro

205 210 215

ggg aag agc ttc cag cag tcc cat gtg cac gtc cat gac ttg cag agc 723

Gly Lys Ser Phe Gln Gln Ser His Val His Val His Asp Leu Gln Ser

220 225 230

ttt ggc ctt gac aac atc aac atg acc cac tac atc cag cac ctg tca 771

Phe Gly Leu Asp Asn Ile Asn Met Thr His Tyr Ile Gln His Leu Ser

235 240 245 250

ttt ggg gag gac tat cca ggc att gtg aac ccc ctg gac cac acc aat 819

Phe Gly Glu Asp Tyr Pro Gly Ile Val Asn Pro Leu Asp His Thr Asn

255 260 265

gtc act gcg ccc caa gcc tcc atg atg ttc cag tac ttt gtg aag gtg 867

Val Thr Ala Pro Gln Ala Ser Met Met Phe Gln Tyr Phe Val Lys Val

270 275 280

gtg ccc act gtg tac atg aag gtg gac gga gag gta ctg agg aca aat 915

Val Pro Thr Val Tyr Met Lys Val Asp Gly Glu Val Leu Arg Thr Asn

285 290 295

cag ttc tct gtg acc aga cat gag aag gtt gcc aat ggg ctg ttg ggc 963

Gln Phe Ser Val Thr Arg His Glu Lys Val Ala Asn Gly Leu Leu Gly

300 305 310

gac caa ggc ctt ccc gga gtc ttc gtc ctc tat gag ctc tcg ccc atg 1011

Asp Gln Gly Leu Pro Gly Val Phe Val Leu Tyr Glu Leu Ser Pro Met

315 320 325 330

atg gtg aag ctg acg gag aag cac agg tcc ttc acc cac ttc ctg aca 1059

Met Val Lys Leu Thr Glu Lys His Arg Ser Phe Thr His Phe Leu Thr

335 340 345

ggt gtg tgc gcc atc att ggg ggc atg ttc aca gtg gct gga ctc atc 1107

Gly Val Cys Ala Ile Ile Gly Gly Met Phe Thr Val Ala Gly Leu Ile

350 355 360

gat tcg ctc atc tac cac tca gca cga gcc atc cag aag aaa att gat 1155

Asp Ser Leu Ile Tyr His Ser Ala Arg Ala Ile Gln Lys Lys Ile Asp

365 370 375

cta ggg aag aca acg tagtcaccct cggtgcttcc tctgtctcct ctttctccct 1210

Leu Gly Lys Thr Thr

380

ggcctgtggt tgtcccccag cctctgccac cctccacctc ctcggtcagc cccagcccca 1270

ggttgataaa tctattgatt gattgtgata gtaac 1305

<210> 30

<211> 383

<212> PRT

<213> Homo sapiens

<400> 30

Met Glu Ala Leu Gly Lys Leu Lys Gln Phe

1 5 10

Asp Ala Tyr Pro Lys Thr Leu Glu Asp Phe Arg Val Lys Thr Cys Gly

15 20 25

Gly Ala Thr Val Thr Ile Val Ser Gly Leu Leu Met Leu Leu Leu Phe
30 35 40
Leu Ser Glu Leu Gln Tyr Tyr Leu Thr Thr Glu Val His Pro Glu Leu
45 50 55
Tyr Val Asp Lys Ser Arg Gly Asp Lys Leu Lys Ile Asn Ile Asp Val
60 65 70
Leu Phe Pro His Met Pro Cys Ala Tyr Leu Ser Ile Asp Ala Met Asp
75 80 85 90
Val Ala Gly Glu Gln Gln Leu Asp Val Glu His Asn Leu Phe Lys Gln
95 100 105
Arg Leu Asp Lys Asp Gly Ile Pro Val Ser Ser Glu Ala Glu Arg His
110 115 120
Glu Leu Gly Lys Val Glu Val Thr Val Phe Asp Pro Asp Ser Leu Asp
125 130 135
Pro Asp Arg Cys Glu Ser Cys Tyr Gly Ala Glu Ala Glu Asp Ile Lys
140 145 150
Cys Cys Asn Thr Cys Glu Asp Val Arg Glu Ala Tyr Arg Arg Arg Gly
155 160 165 170
Trp Ala Phe Lys Asn Pro Asp Thr Ile Glu Gln Cys Arg Arg Glu Gly
175 180 185
Phe Ser Gln Lys Met Gln Glu Gln Lys Asn Glu Gly Cys Gln Val Tyr
190 195 200
Gly Phe Leu Glu Val Asn Lys Val Ala Gly Asn Phe His Phe Ala Pro
205 210 215
Gly Lys Ser Phe Gln Gln Ser His Val His Val His Asp Leu Gln Ser
220 225 230
Phe Gly Leu Asp Asn Ile Asn Met Thr His Tyr Ile Gln His Leu Ser

235 240 245 250

Phe Gly Glu Asp Tyr Pro Gly Ile Val Asn Pro Leu Asp His Thr Asn

255 260 265

Val Thr Ala Pro Gln Ala Ser Met Met Phe Gln Tyr Phe Val Lys Val

270 275 280

Val Pro Thr Val Tyr Met Lys Val Asp Gly Glu Val Leu Arg Thr Asn

285 290 295

Gln Phe Ser Val Thr Arg His Glu Lys Val Ala Asn Gly Leu Leu Gly

300 305 310

Asp Gln Gly Leu Pro Gly Val Phe Val Leu Tyr Glu Leu Ser Pro Met

315 320 325 330

Met Val Lys Leu Thr Glu Lys His Arg Ser Phe Thr His Phe Leu Thr

335 340 345

Gly Val Cys Ala Ile Ile Gly Gly Met Phe Thr Val Ala Gly Leu Ile

350 355 360

Asp Ser Leu Ile Tyr His Ser Ala Arg Ala Ile Gln Lys Lys Ile Asp

365 370 375

Leu Gly Lys Thr Thr

380

<210> 31

<211> 899

<212> DNA

<213> Homo sapiens

<400> 31

cgtcggtgac ctgtgggact cgagctattc ctgcagctca gcagacctcc tggccgtggc 60

agacttctgc gtt atg acc cgg ctg ctg ggc tac gtg gac ccc ctg gat 109

Met Thr Arg Leu Leu Gly Tyr Val Asp Pro Leu Asp

1 5 10

ccc agc ttt gtg gct gcc gtc atc acc atc acc ttc aat ccg ctc tac 157

Pro Ser Phe Val Ala Ala Val Ile Thr Ile Thr Phe Asn Pro Leu Tyr

15 20 25

tgg aat gtg gtt gca cga tgg gaa cac aag acc cgc aag ctg agc agg 205

Trp Asn Val Val Ala Arg Trp Glu His Lys Thr Arg Lys Leu Ser Arg

30 35 40

gcc ttc gga tcc ccc tac ctg gcc tgc tac tct cta agc gtc acc atc 253

Ala Phe Gly Ser Pro Tyr Leu Ala Cys Tyr Ser Leu Ser Val Thr Ile

45 50 55 60

ctg ctc ctg aac ttc ctg cgc tcg cac tgc ttc acg cag gcc atg ctg 301

Leu Leu Leu Asn Phe Leu Arg Ser His Cys Phe Thr Gln Ala Met Leu

65 70 75

agc cag ccc agg atg gag agc ctg gac acc ccc gcg gcc tac agc ctg 349

Ser Gln Pro Arg Met Glu Ser Leu Asp Thr Pro Ala Ala Tyr Ser Leu

80 85 90

ggc ctc gcg ctc ctg gga ctg ggc gtc gtg ctc gtg ctc tcc agc ttc 397

Gly Leu Ala Leu Leu Gly Leu Gly Val Val Leu Val Leu Ser Ser Phe

95 100 105

ttt gca ctg ggg ttc gct gga act ttc cta ggt gat tac ttc ggg atc 445

Phe Ala Leu Gly Phe Ala Gly Thr Phe Leu Gly Asp Tyr Phe Gly Ile

110 115 120

ctc aag gag gcg aga gtg acc gtg ttc ccc ttc aac atc ctg gac aac 493

Leu Lys Glu Ala Arg Val Thr Val Phe Pro Phe Asn Ile Leu Asp Asn

125 130 135 140

ccc atg tac tgg gga agc aca gcc aac tac ctg ggc tgg gcc atc atg 541

Pro Met Tyr Trp Gly Ser Thr Ala Asn Tyr Leu Gly Trp Ala Ile Met

145 150 155

cac gcc agc ccc acg ggc ctg ctc ctg acg gtg ctg gtg gcc ctc acc 589

His Ala Ser Pro Thr Gly Leu Leu Leu Thr Val Leu Val Ala Leu Thr

160 165 170

tac ata gtg gct ctc cta tac gaa gag ccc ttc acc gct gag atc tac 637

Tyr Ile Val Ala Leu Leu Tyr Glu Glu Pro Phe Thr Ala Glu Ile Tyr

175 180 185

cgg cag aaa gcc tcc ggg tcc cac aag agg agc tgattgagct gcaacagctt 690

Arg Gln Lys Ala Ser Gly Ser His Lys Arg Ser

190 195

tgctgaaggc ctggccagcc tcctggcctg ccccaagtgg caggccctgc gcagggcgag 750

aatggtgcct gctgctcagg gctcgccccc ggcgtgggct gccccagtgc cttggaacct 810

gctgccttgg ggaccctgga cgtgccgaca tatggccatt gagctccaac ccacacattc 870

ccattcacca ataaaggcac cctgacccc 899

<210> 32

<211> 199

<212> PRT

<213> Homo sapiens

<400> 32

Met Thr Arg Leu Leu Gly Tyr Val Asp Pro Leu Asp

1 5 10

Pro Ser Phe Val Ala Ala Val Ile Thr Ile Thr Phe Asn Pro Leu Tyr

15 20 25

Trp Asn Val Val Ala Arg Trp Glu His Lys Thr Arg Lys Leu Ser Arg

30 35 40

Ala Phe Gly Ser Pro Tyr Leu Ala Cys Tyr Ser Leu Ser Val Thr Ile

45 50 55 60

Leu Leu Leu Asn Phe Leu Arg Ser His Cys Phe Thr Gln Ala Met Leu

65 70 75

Ser Gln Pro Arg Met Glu Ser Leu Asp Thr Pro Ala Ala Tyr Ser Leu

80 85 90

Gly Leu Ala Leu Leu Gly Leu Gly Val Val Leu Val Leu Ser Ser Phe

95 100 105

Phe Ala Leu Gly Phe Ala Gly Thr Phe Leu Gly Asp Tyr Phe Gly Ile

110 115 120

Leu Lys Glu Ala Arg Val Thr Val Phe Pro Phe Asn Ile Leu Asp Asn

125 130 135 140

Pro Met Tyr Trp Gly Ser Thr Ala Asn Tyr Leu Gly Trp Ala Ile Met

145 150 155

His Ala Ser Pro Thr Gly Leu Leu Leu Thr Val Leu Val Ala Leu Thr

160 165 170

Tyr Ile Val Ala Leu Leu Tyr Glu Glu Pro Phe Thr Ala Glu Ile Tyr

175 180 185

Arg Gln Lys Ala Ser Gly Ser His Lys Arg Ser

190 195

<210> 33

<211> 905

<212> DNA

<213> Homo sapiens

<400> 33

aacggaaa atg gcg cct cac ggc ccg ggt agt ctt acg acc ctg gtg ccc 50

Met Ala Pro His Gly Pro Gly Ser Leu Thr Thr Leu Val Pro

1 5 10

tgg gct gcc gcc ctg ctc ctc gct ctg ggc gtg gaa agg gct ctg gcg 98

Trp Ala Ala Ala Leu Leu Leu Ala Leu Gly Val Glu Arg Ala Leu Ala

15 20 25 30

cta ccc gag ata tgc acc caa tgt cca ggg agc gtg caa aat ttg tca 146

Leu Pro Glu Ile Cys Thr Gln Cys Pro Gly Ser Val Gln Asn Leu Ser

35 40 45

aaa gtg gcc ttt tat tgt aaa acg aca cga gag cta atg ctg cat gcc 194

Lys Val Ala Phe Tyr Cys Lys Thr Thr Arg Glu Leu Met Leu His Ala

50 55 60

cgt tgc tgc ctg aat cag aag ggc acc atc ttg ggg ctg gat ctc cag 242

Arg Cys Cys Leu Asn Gln Lys Gly Thr Ile Leu Gly Leu Asp Leu Gln

65 70 75

aac tgt tct ctg gag gac cct ggt cca aac ttt cat cag gca cat acc 290

Asn Cys Ser Leu Glu Asp Pro Gly Pro Asn Phe His Gln Ala His Thr

80 85 90

act gtc atc ata gac ctg caa gca aac ccc ctc aaa ggt gac ttg gcc 338

Thr Val Ile Ile Asp Leu Gln Ala Asn Pro Leu Lys Gly Asp Leu Ala

95 100 105 110

aac acc ttc cgt ggc ttt act cag ctc cag act ctg ata ctg cca caa 386

Asn Thr Phe Arg Gly Phe Thr Gln Leu Gln Thr Leu Ile Leu Pro Gln

115 120 125

cat gtc aac tgt cct gga gga att aat gcc tgg aat act atc acc tct 434

His Val Asn Cys Pro Gly Gly Ile Asn Ala Trp Asn Thr Ile Thr Ser

130 135 140

tat ata gac aac caa atc tgt caa ggg caa aag aac ctt tgc aat aac 482

Tyr Ile Asp Asn Gln Ile Cys Gln Gly Gln Lys Asn Leu Cys Asn Asn

145 150 155

act ggg gac cca gaa atg tgt cct gag aat gga tct tgt gta cct gat 530

Thr Gly Asp Pro Glu Met Cys Pro Glu Asn Gly Ser Cys Val Pro Asp

160 165 170

ggt cca ggt ctt ttg cag tgt gtt tgt gct gat ggt ttc cat gga tac 578

Gly Pro Gly Leu Leu Gln Cys Val Cys Ala Asp Gly Phe His Gly Tyr

175 180 185 190

aag tgt atg cgc cag ggc tcg ttc tca ctg ctt atg ttc ttc ggg att 626

Lys Cys Met Arg Gln Gly Ser Phe Ser Leu Leu Met Phe Phe Gly Ile

195 200 205

ctg gga gcc acc act cta tcc gtc tcc att ctg ctt tgg gcg acc cag 674

Leu Gly Ala Thr Thr Leu Ser Val Ser Ile Leu Leu Trp Ala Thr Gln

210 215 220

cgc cga aaa gcc aag act tca tgaac tacataggtc ttaccattga 720

Arg Arg Lys Ala Lys Thr Ser

225

cctaagatca atctgaacta tcttagccca gtcagggagc tctgcttcct agaaaggcat 780

ctttcgccag tggattcgcc tcaaggttga ggccgccatt ggaagatgaa aaattgcact 840

cccttggtgt agacaaatac cagttcccat tggtgttgtt gcctataata aacacttttt 900

ctttt 905

<210> 34

<211> 229

<212> PRT

<213> Homo sapiens

<400> 34

Met Ala Pro His Gly Pro Gly Ser Leu Thr Thr Leu Val Pro
1 5 10

Trp Ala Ala Ala Leu Leu Leu Ala Leu Gly Val Glu Arg Ala Leu Ala
15 20 25 30

Leu Pro Glu Ile Cys Thr Gln Cys Pro Gly Ser Val Gln Asn Leu Ser
35 40 45

Lys Val Ala Phe Tyr Cys Lys Thr Thr Arg Glu Leu Met Leu His Ala
50 55 60

Arg Cys Cys Leu Asn Gln Lys Gly Thr Ile Leu Gly Leu Asp Leu Gln
65 70 75

Asn Cys Ser Leu Glu Asp Pro Gly Pro Asn Phe His Gln Ala His Thr
80 85 90

Thr Val Ile Ile Asp Leu Gln Ala Asn Pro Leu Lys Gly Asp Leu Ala
95 100 105 110

Asn Thr Phe Arg Gly Phe Thr Gln Leu Gln Thr Leu Ile Leu Pro Gln
115 120 125

His Val Asn Cys Pro Gly Gly Ile Asn Ala Trp Asn Thr Ile Thr Ser
130 135 140

Tyr Ile Asp Asn Gln Ile Cys Gln Gly Gln Lys Asn Leu Cys Asn Asn

145 150 155

Thr Gly Asp Pro Glu Met Cys Pro Glu Asn Gly Ser Cys Val Pro Asp

160 165 170

Gly Pro Gly Leu Leu Gln Cys Val Cys Ala Asp Gly Phe His Gly Tyr

175 180 185 190

Lys Cys Met Arg Gln Gly Ser Phe Ser Leu Leu Met Phe Phe Gly Ile

195 200 205

Leu Gly Ala Thr Thr Leu Ser Val Ser Ile Leu Leu Trp Ala Thr Gln

210 215 220

Arg Arg Lys Ala Lys Thr Ser

225

<210> 35

<211> 841

<212> DNA

<213> Homo sapiens

<400> 35

ctccacgagg ctgccggctt aggaccccca gctccgac atg tcg ccc tct ggt cgc 56

Met Ser Pro Ser Gly Arg

1 5

ctg tgt ctt ctc acc atc gtt ggc ctg att ctc ccc acc aga gga cag 104

Leu Cys Leu Leu Thr Ile Val Gly Leu Ile Leu Pro Thr Arg Gly Gln

10 15 20

acg ttg aaa gat acc acg tcc agt tct tca gca gac tca act atc atg 152

Thr Leu Lys Asp Thr Thr Ser Ser Ser Ser Ala Asp Ser Thr Ile Met

25 30 35

gac att cag gtc ccg aca cga gcc cca gat gca gtc tac aca gaa ctc 200

Asp Ile Gln Val Pro Thr Arg Ala Pro Asp Ala Val Tyr Thr Glu Leu

40 45 50

cag ccc acc tct cca acc cca acc tgg cct gct gat gaa aca cca caa 248

Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro Ala Asp Glu Thr Pro Gln

55 60 65 70

ccc cag acc cag acc cag caa ctg gaa gga acg gat ggg cct cta gtg 296

Pro Gln Thr Gln Thr Gln Gln Leu Glu Gly Thr Asp Gly Pro Leu Val

75 80 85

aca gat cca gag aca cac aag agc acc aaa gca gct cat ccc act gat 344

Thr Asp Pro Glu Thr His Lys Ser Thr Lys Ala Ala His Pro Thr Asp

90 95 100

gac acc acg acg ctc tct gag aga cca tcc cca agc aca gac gtc cag 392

Asp Thr Thr Thr Leu Ser Glu Arg Pro Ser Pro Ser Thr Asp Val Gln

105 110 115

aca gac ccc cag acc ctc aag cca tct ggt ttt cat gag gat gac ccc 440

Thr Asp Pro Gln Thr Leu Lys Pro Ser Gly Phe His Glu Asp Asp Pro

120 125 130

ttc ttc tat gat gaa cac acc ctc cgg aaa cgg ggg ctg ttg gtc gca 488

Phe Phe Tyr Asp Glu His Thr Leu Arg Lys Arg Gly Leu Leu Val Ala

135 140 145 150

gct gtg ctg ttc atc aca ggc atc atc atc ctc acc agt ggc aag tgc 536

Ala Val Leu Phe Ile Thr Gly Ile Ile Ile Leu Thr Ser Gly Lys Cys

155 160 165

agg cag ctg tcc cgg tta tgc cgg aat cat tgc agg tgagtcca 580

Arg Gln Leu Ser Arg Leu Cys Arg Asn His Cys Arg

170 175

tcagaaacag gagctgacaa cccgctgggc acccgaagac caagcccccct gccagctcac 640

cgtgcccagc ctcctgcatc ccctcgaaga gcctggccag agagggaaga cacagatgat 700

gaagctggag ccagggctgc cggtccgagt ctcctacctc ccccaacccct gcccgcccct 760

gaaggctacc tggcgccttg gggctgtcc ctcaagttat ctcctctgtt aagacaaaaa 820

gtaaagcact gtggtctttg c 841

<210> 36

<211> 178

<212> PRT

<213> Homo sapiens

<400> 36

Met Ser Pro Ser Gly Arg

1 5

Leu Cys Leu Leu Thr Ile Val Gly Leu Ile Leu Pro Thr Arg Gly Gln

10 15 20

Thr Leu Lys Asp Thr Thr Ser Ser Ser Ser Ala Asp Ser Thr Ile Met

25 30 35

Asp Ile Gln Val Pro Thr Arg Ala Pro Asp Ala Val Tyr Thr Glu Leu

40 45 50

Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro Ala Asp Glu Thr Pro Gln

55 60 65 70

Pro Gln Thr Gln Thr Gln Gln Leu Glu Gly Thr Asp Gly Pro Leu Val

75 80 85

Thr Asp Pro Glu Thr His Lys Ser Thr Lys Ala Ala His Pro Thr Asp

90 95 100

Asp Thr Thr Thr Leu Ser Glu Arg Pro Ser Pro Ser Thr Asp Val Gln

105 110 115

Thr Asp Pro Gln Thr Leu Lys Pro Ser Gly Phe His Glu Asp Asp Pro

120 125 130

Phe Phe Tyr Asp Glu His Thr Leu Arg Lys Arg Gly Leu Leu Val Ala

135 140 145 150

Ala Val Leu Phe Ile Thr Gly Ile Ile Ile Leu Thr Ser Gly Lys Cys

155 160 165

Arg Gln Leu Ser Arg Leu Cys Arg Asn His Cys Arg

170 175

<210> 37

<211> 1451

<212> DNA

<213> Homo sapiens

<400> 37

actgcctgga aacgggctgg gcctgcctcg gacgccgccg gtgtcgcgga ttctctttcc 60

gcccgctcca tggcggtgga tgcctgactg gaagcccgag tggg atg cgg ctg acg 116

Met Arg Leu Thr

1

cgg aag cgg ctc tgc tcg ttt ctt atc gcc ctg tac tgc cta ttc tcc 164

Arg Lys Arg Leu Cys Ser Phe Leu Ile Ala Leu Tyr Cys Leu Phe Ser

5 10 15 20

ctc tac gct gcc tac cac gtc ttc ttc ggg cgc cgc cgc cag gcg ccg 212

Leu Tyr Ala Ala Tyr His Val Phe Phe Gly Arg Arg Arg Gln Ala Pro

25 30 35

gcc ggg tcc ccg cgg ggc ctc agg aag ggg gcg gcc ccc gcg cgg gag 260

Ala Gly Ser Pro Arg Gly Leu Arg Lys Gly Ala Ala Pro Ala Arg Glu

40 45 50

aga cgc ggc cga gaa cag tcc act ttg gaa agt gaa gaa tgg aat cct 308

Arg Arg Gly Arg Glu Gln Ser Thr Leu Glu Ser Glu Glu Trp Asn Pro

55 60 65

tgg gaa gga gat gaa aaa aat gag caa caa cac aga ttt aaa act agc 356

Trp Glu Gly Asp Glu Lys Asn Glu Gln Gln His Arg Phe Lys Thr Ser

70 75 80

ctt caa ata tta gat aaa tcc acg aaa gga aaa aca gat ctc agt gta 404

Leu Gln Ile Leu Asp Lys Ser Thr Lys Gly Lys Thr Asp Leu Ser Val

85 90 95 100

caa atc tgg ggc aaa gct gcc att ggc ttg tat ctc tgg gag cat att 452

Gln Ile Trp Gly Lys Ala Ala Ile Gly Leu Tyr Leu Trp Glu His Ile

105 110 115

ttt gaa ggc tta ctt gat ccc agc gat gtg act gct caa tgg aga gaa 500

Phe Glu Gly Leu Leu Asp Pro Ser Asp Val Thr Ala Gln Trp Arg Glu

120 125 130

gga aag tca atc gta gga aga aca cag tac agc ttc atc act ggt cca 548

Gly Lys Ser Ile Val Gly Arg Thr Gln Tyr Ser Phe Ile Thr Gly Pro

135 140 145

gct gta ata cca ggg tac ttc tcc gtt gat gtg aat aat gtg gta ctc 596

Ala Val Ile Pro Gly Tyr Phe Ser Val Asp Val Asn Asn Val Val Leu

150 155 160

att tta aat gga aga gaa aaa gca aag atc ttt tat gcc acc cag tgg 644

ile leu asn gly arg glu lys ala lys ile phe tyr ala thr gln trp
165 170 175 180
tta ctt tat gca caa aat tta gtg caa att caa aaa ctc cag cat ctt 692
Leu Leu Tyr Ala Gln Asn Leu Val Gln Ile Gln Lys Leu Gln His Leu
185 190 195
gct gtt gtt ttg ctc gga aat gaa cat tgt gat aat gag tgg ata aac 740
Ala Val Val Leu Leu Gly Asn Glu His Cys Asp Asn Glu Trp Ile Asn
200 205 210
cca ttc ctc aaa aga aat gga ggc ttc gtg gag ctg ctt ttc ata ata 788
Pro Phe Leu Lys Arg Asn Gly Gly Phe Val Glu Leu Leu Phe Ile Ile
215 220 225
tat gac agc ccc tgg att aat gac gtg gat gtt ttt cag tgg cct tta 836
Tyr Asp Ser Pro Trp Ile Asn Asp Val Asp Val Phe Gln Trp Pro Leu
230 235 240
gga gta gca aca tac agg aat ttt cct gtg gtg gag gca agt tgg tca 884
Gly Val Ala Thr Tyr Arg Asn Phe Pro Val Val Glu Ala Ser Trp Ser
245 250 255 260
atg ctg cat gat gag agg cca tat tta tgt aat ttc tta gga acg att 932
Met Leu His Asp Glu Arg Pro Tyr Leu Cys Asn Phe Leu Gly Thr Ile
265 270 275
tat gaa aat tca tcc aga cag gca cta atg aac att ttg aaa aaa gat 980
Tyr Glu Asn Ser Ser Arg Gln Ala Leu Met Asn Ile Leu Lys Lys Asp
280 285 290
ggg aac gat aag ctt tgt tgg gtt tca gca aga gaa cac tgg cag cct 1028
Gly Asn Asp Lys Leu Cys Trp Val Ser Ala Arg Glu His Trp Gln Pro
295 300 305
cag gaa aca aat gaa agt ctt aag aat tac caa gat gcc ttg ctt cag 1076

Gln Glu Thr Asn Glu Ser Leu Lys Asn Tyr Gln Asp Ala Leu Leu Gln

310 315 320

agt gat ctc aca ttg tgc ccg gtc gga gta aac aca gaa tgc tat cga 1124

Ser Asp Leu Thr Leu Cys Pro Val Gly Val Asn Thr Glu Cys Tyr Arg

325 330 335 340

atc tat gag gct tgc tcc tat ggc tcc att cct gtg gtg gaa gac gtg 1172

Ile Tyr Glu Ala Cys Ser Tyr Gly Ser Ile Pro Val Val Glu Asp Val

345 350 355

atg aca gct ggc aac tgt ggg aat aca tct gtg cac cac ggt gct cct 1220

Met Thr Ala Gly Asn Cys Gly Asn Thr Ser Val His His Gly Ala Pro

360 365 370

ctg cag tta ctc aag tcc atg ggt gct ccc ttt atc ttt atc aag aac 1268

Leu Gln Leu Leu Lys Ser Met Gly Ala Pro Phe Ile Phe Ile Lys Asn

375 380 385

tgg aag gaa ctc cct gct gtt tta gaa aaa gag aaa act ata att tta 1316

Trp Lys Glu Leu Pro Ala Val Leu Glu Lys Glu Lys Thr Ile Ile Leu

390 395 400

caa gaa aaa att gaa aga aga aaa atg tta ctt cag tgg tat cag cac 1364

Gln Glu Lys Ile Glu Arg Arg Lys Met Leu Leu Gln Trp Tyr Gln His

405 410 415 420

ttc aag aca gag ctt aaa atg aaa ttt act aat att tta gaa agc tca 1412

Phe Lys Thr Glu Leu Lys Met Lys Phe Thr Asn Ile Leu Glu Ser Ser

425 430 435

ttt tta atg aat aat aaa agt taattat ctttttgagc t 1451

Phe Leu Met Asn Asn Lys Ser

440

<210> 38

<211> 443

<212> PRT

<213> Homo sapiens

<400> 38

Met Arg Leu Thr

1

Arg Lys Arg Leu Cys Ser Phe Leu Ile Ala Leu Tyr Cys Leu Phe Ser

5 10 15 20

Leu Tyr Ala Ala Tyr His Val Phe Phe Gly Arg Arg Arg Gln Ala Pro

25 30 35

Ala Gly Ser Pro Arg Gly Leu Arg Lys Gly Ala Ala Pro Ala Arg Glu

40 45 50

Arg Arg Gly Arg Glu Gln Ser Thr Leu Glu Ser Glu Glu Trp Asn Pro

55 60 65

Trp Glu Gly Asp Glu Lys Asn Glu Gln Gln His Arg Phe Lys Thr Ser

70 75 80

Leu Gln Ile Leu Asp Lys Ser Thr Lys Gly Lys Thr Asp Leu Ser Val

85 90 95 100

Gln Ile Trp Gly Lys Ala Ala Ile Gly Leu Tyr Leu Trp Glu His Ile

105 110 115

Phe Glu Gly Leu Leu Asp Pro Ser Asp Val Thr Ala Gln Trp Arg Glu

120 125 130

Gly Lys Ser Ile Val Gly Arg Thr Gln Tyr Ser Phe Ile Thr Gly Pro

135 140 145

Ala Val Ile Pro Gly Tyr Phe Ser Val Asp Val Asn Asn Val Val Leu
150 155 160
Ile Leu Asn Gly Arg Glu Lys Ala Lys Ile Phe Tyr Ala Thr Gln Trp
165 170 175 180
Leu Leu Tyr Ala Gln Asn Leu Val Gln Ile Gln Lys Leu Gln His Leu
185 190 195
Ala Val Val Leu Leu Gly Asn Glu His Cys Asp Asn Glu Trp Ile Asn
200 205 210
Pro Phe Leu Lys Arg Asn Gly Gly Phe Val Glu Leu Leu Phe Ile Ile
215 220 225
Tyr Asp Ser Pro Trp Ile Asn Asp Val Asp Val Phe Gln Trp Pro Leu
230 235 240
Gly Val Ala Thr Tyr Arg Asn Phe Pro Val Val Glu Ala Ser Trp Ser
245 250 255 260
Met Leu His Asp Glu Arg Pro Tyr Leu Cys Asn Phe Leu Gly Thr Ile
265 270 275
Tyr Glu Asn Ser Ser Arg Gln Ala Leu Met Asn Ile Leu Lys Lys Asp
280 285 290
Gly Asn Asp Lys Leu Cys Trp Val Ser Ala Arg Glu His Trp Gln Pro
295 300 305
Gln Glu Thr Asn Glu Ser Leu Lys Asn Tyr Gln Asp Ala Leu Leu Gln
310 315 320
Ser Asp Leu Thr Leu Cys Pro Val Gly Val Asn Thr Glu Cys Tyr Arg
325 330 335 340
Ile Tyr Glu Ala Cys Ser Tyr Gly Ser Ile Pro Val Val Glu Asp Val
345 350 355
Met Thr Ala Gly Asn Cys Gly Asn Thr Ser Val His His Gly Ala Pro

360 365 370

Leu Gln Leu Leu Lys Ser Met Gly Ala Pro Phe Ile Phe Ile Lys Asn

375 380 385

Trp Lys Glu Leu Pro Ala Val Leu Glu Lys Glu Lys Thr Ile Ile Leu

390 395 400

Gln Glu Lys Ile Glu Arg Arg Lys Met Leu Leu Gln Trp Tyr Gln His

405 410 415 420

Phe Lys Thr Glu Leu Lys Met Lys Phe Thr Asn Ile Leu Glu Ser Ser

425 430 435

Phe Leu Met Asn Asn Lys Ser

440

<210> 39

<211> 886

<212> DNA

<213> Homo sapiens

<400> 39

accaaacctg tggacgccga cccgggaccg ccgctggctg gctgctggct cactcgaccg 60

tc atg gag acc ctg ggg gcc ctt ctg gtg ctg gag ttt ctg ctc ctc 107

Met Glu Thr Leu Gly Ala Leu Leu Val Leu Glu Phe Leu Leu Leu

1 5 10 15

tcc ccg gtg gag gcc cag cag gcc acg gag cat cgc ctg aag ccg tgg 155

Ser Pro Val Glu Ala Gln Gln Ala Thr Glu His Arg Leu Lys Pro Trp

20 25 30

ctg gtg ggc ctg gct gcg gta gtc ggc ttc ctg ttc atc gtc tat ttg 203

Leu Val Gly Leu Ala Ala Val Val Gly Phe Leu Phe Ile Val Tyr Leu

35 40 45

gtc ttg ctg gcc aac cgc ctc tgg tgt tcc aag gcc agg gct gag gac 251

Val Leu Leu Ala Asn Arg Leu Trp Cys Ser Lys Ala Arg Ala Glu Asp

50 55 60

gag gag gag acc acg ttc aga atg gag tcc aac cta tac cag gac cag 299

Glu Glu Glu Thr Thr Phe Arg Met Glu Ser Asn Leu Tyr Gln Asp Gln

65 70 75

agt gaa gac aag aga gag aag aaa gag gcc aag gag aaa gaa gag aag 347

Ser Glu Asp Lys Arg Glu Lys Lys Glu Ala Lys Glu Lys Glu Glu Lys

80 85 90 95

agg aag aag gag aaa aag aca gca aag gaa gga gag agc aac ttg gga 395

Arg Lys Lys Glu Lys Lys Thr Ala Lys Glu Gly Glu Ser Asn Leu Gly

100 105 110

ctg gat ctg gag gaa aaa gag ccc gga gac cat gag aga gca aag agc 443

Leu Asp Leu Glu Glu Lys Glu Pro Gly Asp His Glu Arg Ala Lys Ser

115 120 125

aca gtc atg tgaagatt cctggctgcc tcttccaggc agtcccccag agatgcctct 500

Thr Val Met

130

tctgcccccct aaaagcagtg ccctggactt gaagcccgtg aaatgactcc atctgggatt 560

cagaatacag tgttctcaag tgaagaaggc ttggaaccca ccccacctcc ctcattgggg 620

gctctctggg caaacatggt tttcatgcac ccctcttcct gagcttggtc cctgcctggt 680

gattcttctt atactcggag agcatccctg gttgaggaga caccccgcaat cctccacgat 740

ctcatggctc cacctgcttc tccccactgc ctgatttctt ttctctctgc ctgatgtcta 800

ctgaacagaa cttcccctct cccatgcacc cactgccagc tgagagctgc ttcccaatgg 860

cctgcattaa agcattcgta acagcc 886

<210> 40

<211> 130

<212> PRT

<213> Homo sapiens

<400> 40

Met Glu Thr Leu Gly Ala Leu Leu Val Leu Glu Phe Leu Leu Leu
1 5 10 15

Ser Pro Val Glu Ala Gln Gln Ala Thr Glu His Arg Leu Lys Pro Trp
20 25 30

Leu Val Gly Leu Ala Ala Val Val Gly Phe Leu Phe Ile Val Tyr Leu
35 40 45

Val Leu Leu Ala Asn Arg Leu Trp Cys Ser Lys Ala Arg Ala Glu Asp
50 55 60

Glu Glu Glu Thr Thr Phe Arg Met Glu Ser Asn Leu Tyr Gln Asp Gln
65 70 75

Ser Glu Asp Lys Arg Glu Lys Lys Glu Ala Lys Glu Lys Glu Glu Lys
80 85 90 95

Arg Lys Lys Glu Lys Lys Thr Ala Lys Glu Gly Glu Ser Asn Leu Gly
100 105 110

Leu Asp Leu Glu Glu Lys Glu Pro Gly Asp His Glu Arg Ala Lys Ser
115 120 125

Thr Val Met
130

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C12N 15/12, C07K 14/47, C12N 15/79, 5/10	A3	(11) International Publication Number: WO 99/18203 (43) International Publication Date: 15 April 1999 (15.04.99)

(21) International Application Number: PCT/JP98/04475

(22) International Filing Date: 5 October 1998 (05.10.98)

(30) Priority Data:
9/276271 8 October 1997 (08.10.97) JP

(71) Applicants *(for all designated States except US)*: SAGAMI CHEMICAL RESEARCH CENTER [JP/JP]; 4-1, Nishi-Ohnuma 4-chome, Sagamihara-shi, Kanagawa 229-0012 (JP). PROTEGENE INC. [JP/JP]; 2-20-3, Naka-cho, Meguro-ku, Tokyo 153-0065 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: KATO, Seishi [JP/JP]; 3-46-50, Wakamatsu, Sagamihara-shi, Kanagawa 229-0014 (JP). YAMAGUCHI, Tomoko [JP/JP]; 5-13-11, Takasago, Katsushika-ku, Tokyo 125-0054 (JP). SEKINE, Shingo [JP/JP]; Remonzu 101, 2-8-15, Atago, Ageo-shi, Saitama 362-0034 (JP). KOBAYASHI, Midori [JP/JP]; Royal Court 306, 3-2-3, Minami-Rinkan, Yamato-shi, Kanagawa 242-0006 (JP).

(74) Agents: AOYAMA, Tamotsu et al.; Aoyama & Partners, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 540-0001 (JP).

(81) Designated States: AU, CA, JP, MX, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(88) Date of publication of the international search report: 24 June 1999 (24.06.99)

(54) Title: HUMAN PROTEINS HAVING TRANSMEMBRANE DOMAINS AND cDNAs ENCODING THESE PROTEINS

(57) Abstract

The invention provides human proteins having transmembrane domains and cDNAs coding for these proteins as well as eukaryotic cells expressing said cDNAs. All of the proteins exist in the cell membrane, so that they are considered to be proteins controlling the proliferation and the differentiation of the cells. Accordingly, the proteins can be employed as pharmaceuticals such as carcinostatic agents relating to the control of the proliferation and the differentiation of the cells or as antigens for preparing antibodies against said proteins. The cDNAs can be utilized as probes for the gene diagnosis and gene sources for the gene therapy. Furthermore, the cDNAs can be utilized for large-scale expression of said proteins. Cells, wherein these membrane protein genes are introduced and membrane proteins are expressed in large amounts, can be utilized for detection of the corresponding ligands, screening of novel low-molecular pharmaceuticals, and so on.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CU	Cuba
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakstan
LC	Saint Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	The former Yugoslav Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 98/04475

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/47 C12N15/79 C12N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Genbank Database Entry GGSCA2A Accession number L34554; 16 July 1994 PETRENKO O. ET AL.:"Characterization of changes in gene expression associated with leukemic transformation by the NK-kB family member v-Rel" XP002089382 cited in the application see the whole document ---	1-6
A	EMBL Database Entry HS1268023 Accession number AA476643; 23 June 1997 HILLIER ET AL.:"WashU-Merck EST Project 1997" XP002089383 cited in the application see the whole document ---	1-6
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 January 1999	23.04.99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	MONTERO LOPEZ B.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 98/04475

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 00540 A (INCYTE PHARMACEUTICALS, INC.) 8 January 1998 see page 2, line 18 - page 3, line 5 see sequences SEQ ID NO:2 and 4 ---	1-3,5,6
P,X	ROBERT E. REITER ET AL.: "Prostate stem cell antigen: A cell surface marker overexpressed in prostate cancer" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 95, no. 4, 17 February 1998, pages 1735-1740, XP002089381 WASHINGTON US see page 1735, right-hand column, paragraph 2; figure 2 ---	1,2,5,6
E	WO 98 51805 A (ABBOTT LABORATORIES) 19 November 1998 see page 5, line 28 - page 6, line 14 see sequences SEQ ID NO:11, 12, 25 ---	1-6
E	WO 98 51824 A (ABBOTT LABORATORIES) 19 November 1998 see page 5, line 8 - line 20 see sequences SEQ ID NO:11, 12, 25 -----	1-6

1

INTERNATIONAL SEARCH REPORT	International application No PCT/JP 98/04475

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-6 partially (subject 1. on continuation-sheet)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-6 partially

   Protein comprising sequence SEQ ID NO:1; DNA encoding it; cDNA comprising SEQ ID NO:11 or 21; vector and host cell capable of expressing the same.

2. Claims: 1-6 partially

   Protein comprising sequence SEQ ID NO:2; DNA encoding it; cDNA comprising SEQ ID NO:12 or 23; vector and host cell capable of expressing the same.

3. Claims: 1-6 partially

   Protein comprising sequence SEQ ID NO:3; DNA encoding it; cDNA comprising SEQ ID NO:13 or 25; vector and host cell capable of expressing the same.

4. Claims: 1-6 partially

   Protein comprising sequence SEQ ID NO:4; DNA encoding it; cDNA comprising SEQ ID NO:14 or 27; vector and host cell capable of expressing the same.

5. Claims: 1-6 partially

   Protein comprising sequence SEQ ID NO:5; DNA encoding it; cDNA comprising SEQ ID NO:15 or 29; vector and host cell capable of expressing the same.

6. Claims: 1-6 partially

   Protein comprising sequence SEQ ID NO:6; DNA encoding it; cDNA comprising SEQ ID NO:16 or 31; vector and host cell capable of expressing the same.

7. Claims: 1-6 partially

   Protein comprising sequence SEQ ID NO:7; DNA encoding it; cDNA comprising SEQ ID NO:17 or 33; vector and host cell capable of expressing the same.

8. Claims: 1-6 partially

   Protein comprising sequence SEQ ID NO:8; DNA encoding it; cDNA comprising SEQ ID NO:18 or 35; vector and host cell capable of expressing the same.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

9. Claims: 1-6 partially

Protein comprising sequence SEQ ID NO:9; DNA encoding it; cDNA comprising SEQ ID NO:19 or 37; vector and host cell capable of expressing the same.

10. Claims: 1-6 partially

Protein comprising sequence SEQ ID NO:10; DNA encoding it; cDNA comprising SEQ ID NO:20 or 39; vector and host cell capable of expressing the same.

INTERNATIONAL SEARCH REPORT

xmation on patent family members

International Application No
PCT/JP 98/04475

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9800540 A	08-01-1998	US 5856136 A	05-01-1999
		AU 3501197 A	21-01-1998
		EP 0909318 A	21-04-1999
WO 9851805 A	19-11-1998	NONE	
WO 9851824 A	19-11-1998	NONE	